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# *Lectures on the Pathology of Cancer*

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# Lectures on the Pathology of Cancer

BY

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# PREFACE.

THESE lectures were delivered in the University of Manchester in June and July, 1908, in connection with the Pilkington Cancer Research Fund. They do not profess to contain the whole pathology of Cancer. My idea has been rather to give a general outline, dealing more particularly with certain points which are neglected, or imperfectly dealt with, in most works on the subject. Hence I have laid particular stress on the life history of tumours, and on certain biological problems connected therewith.

I desire to take this opportunity of expressing my thanks to Mrs. Pilkington, the founder of the Pilkington Cancer Research Fund; and to Professor Lorrain Smith, in whose department my work is carried on.

CHARLES POWELL WHITE.

MANCHESTER,
*October, 1908.*

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# TUMOURS IN GENERAL

# PART I. TUMOURS IN GENERAL.

## Definition.

To understand the pathology of Cancer it is necessary first to know what Cancer is, what its relationship is to other tumours, to other diseases, and to normal tissues.

By Cancer I understand any form of malignant disease. Some authors have attempted to limit the term to Carcinoma but there is no reason for this, and it is more satisfactory to use the compact term Cancer as a synonym for the more cumbrous term Malignant disease.

The cancers are members of the group of disorders known as Tumours which are characterised especially by their progressive and independent growth, and the pathology of Cancer cannot be considered apart from the pathology of other tumours.

The definition and classification of tumours which I adopt is one which I brought forward in the Erasmus Wilson lectures which I delivered before the Royal College of Surgeons in 1902.[10]

A tumour is defined as *a mass of cells, tissues, or organs, resembling those normally present in the body, but arranged atypically, which grows at the expense of the organism without, at the same time, subserving any useful function therein.*

There are two important points in this definition. First, the distinguishing character of a tumour is the fact that it is *atypical,* not in the structure, but in the arrangement of its component parts. This feature distinguishes a tumour from a condition such as hypertrophy. The second point is that a tumour grows at the expense of the organism, but does not subserve any useful function therein. This distinguishes a tumour from an inflammatory mass, which, however destructive it may appear, has a useful tendency and ceases to increase when the irritant which causes it is removed or neutralised.

The normal organism is composed of a number of *organs* of which the structure and arrangement are characteristic for the species but differ in different species.

An organ is composed of a combination of *tissues* of which the structure and arrangement are typical for the organ concerned but differ in different organs.

A tissue is composed of a number of *cells* with more or less intercellular substance, of which the structure and arrangement are typical for each tissue, but differ in different tissues.

If this typical arrangement fail at any point the result is a tumour of some kind.

Thus we may find *organs,* recognisable as such, arranged in an atypical manner as in a *dermoid cyst* in which we can recognise skin, teeth, glands, bones, etc., without any definite arrangement.

Also *fibrous tissue* with its blood-vessels, etc., is normally arranged to form a definite organ—a tendon or fascia. If, however, while retaining its typical characters as fibrous tissue, it is not arranged in a typical manner, but forms an irregular mass we have a tumour—a *fibroma.* Again *fibrous tissue cells* are normally arranged with a certain amount of intercellular substance to form a tissue—*fibrous tissue.* If, however, the cells multiply without forming the intercellular substance the result is a tumour—a *sarcoma.*

To take another example: *epithelium* is normally arranged

in a definite manner together with connective-tissue, blood-vessels, etc., to form an organ, for example, a secreting gland. In an *adenoma,* however, the epithelium and connective-tissue, while themselves resembling normal tissues, are arranged irregularly and not so as to form a gland (Fig. 1). Again, normally *epithelial cells* are arranged in contact with one another forming a membrane which covers a surface or lines tubes and spaces. This membrane is an epithelium—a tissue. If, however, the epithelial cells are not arranged in the typical way but grow irregularly in the connective-tissue spaces not forming a definite membrane, we have a tumour—a *carcinoma* (Fig. 2).

## Classification.

We have, then, the following classification of tumours.

In the first place we have tumours which are composed of more or less definite *organs* which are arranged atypically as in a dermoid. These are called Organ Tumours or Organomata.

In the next place we have tumours which are composed of *tissues* arranged atypically. These are called Tissue Tumours or Histiomata and include the non-malignant tumours.

Lastly we have tumours which are composed of *cells* arranged atypically. These are called Cell Tumours or Cytomata and include the cancers.

In this last group the characteristic feature is to be found in the growing portion of the tumour. Some carcinomata show well formed epithelium and closely resemble adenomata, and some sarcomata contain well formed fibrous tissue, cartilage, etc., but, if the growing part of the tumour be examined the distinction will be found to hold good, the definite tissues being of secondary formation whereas in the histiomata the definite tissues are present in the growing as in the older parts. I shall have more to say on this point when I consider the growth of tumours.

The classification is, then, as in the accompanying table.

## Classification of Tumours.

| | |
|---|---|
| A. ORGANOMATA. | Teratoma. (Dermoid Cyst.) |
| B. HISTIOMATA. | |
| (*a*) Connective tissue tumours. | DESMOMATA. |
| Fibrous tissue, | Fibroma. |
| Fat, | Lipoma. |
| Mucous tissue, | Myxoma. |
| Notochordal tissue, | Chordoma. |
| Cartilage, | Chondroma. |
| Bone, | Osteoma. |
| Neuroglia, | Glioma. |
| (*b*) Lymphoid tissue tumours. | LYMPHOMATA. |
| Lymphadenoid tissue, | Lymphadenoma. (Lymphoma.) |
| Bone marrow, | Myeloma. |
| (*c*) Muscle tumours. | MYOMATA. |
| Smooth muscle, | Leiomyoma. |
| Striated muscle, | Rhabdomyoma. |
| (*d*) Nerve tissue tumours. | NEUROMATA. |
| Medullated Nerve tissue, | Myelinic Neuroma. |
| Nonmedullated nerve tissue, | Amyelinic Neuroma. |
| (*e*) Epithelial tissue tumours. | EPITHELIOMATA. |
| Squamous celled epithelium, | Squamous celled Adenoma.<br>Squamous celled Papilloma. |
| Columnar celled epithelium, | Columnar celled Adenoma.<br>Columnar celled Papilloma. |
| Spheroidal celled epithelium, | Spheroidal celled Adenoma. |
| Endothelium, | Angeioma.<br>Endothelial Papilloma. |
| C. CYTOMATA. | |
| (*a*) Tumours of indifferent cells. (Blastocytes.) | BLASTOCYTOMATA. |
| (*b*) Tumours of connective tissue cells also of lymphoid tissue cells and muscle cells. (Mesocytes.) | SARCOMATA. (Mesocytomata.) |
| (1) Pure Sarcomata. | |
| Round cells, | Round celled Sarcoma. |
| Spindle cells, | Spindle celled Sarcoma. |
| Giant cells, | Giant celled Sarcoma. |
| (2) Compound Sarcomata. | |
| Fibrocytes, | Fibrosarcoma. |
| Chondrocytes, | Chondrosarcoma. |
| etc., etc. | etc., etc. |
| (*c*) Tumours of Epithelial cells. | CARCINOMATA. (Epicytomata.) |
| Squamous epicytes, | Squamous celled Carcinoma. |
| Columnar epicytes, | Columnar celled Carcinoma. |
| Spheroidal epicytes, | Spheroidal celled Carcinoma. |
| Endocytes, | Endothelial celled Carcinoma. |
| Syncytium, | Syncytial Carcinoma. |

This classification has the great advantage that it enables us, if we are sure of what we see with the microscope, to place any given specimen in its proper place. In other words, the

classification is based on facts which can be observed and not on any theories which may vary from time to time. Many attempts have been made by different authors to fashion a classification of tumours on an embryological basis but they all fail when put to the test. To my mind a classification based on embryology is unscientific and useless. A classification should always be based on facts and not on theories. We do not, for instance, classify common objects according to their ultimate derivation but according to their structure or the uses to which they are put. Who, for instance, would classify metal goods according to the mines from which the metallic ore was obtained? Yet this is exactly comparable to a classification of tumours on an embryological basis.

Another advantage of this scheme is the fact that the classes *Histiomata* and *Cytomata* correspond to the classes distinguished clinically as *simple* and *malignant* tumours. Each kind of tissue is represented by a tissue tumour and every kind of cell by a cell tumour.

## Nomenclature.

The different kinds of cells are named by adding the termination *-cyte* to a root expressing the nature of the cell according to the following scheme:—

| | | | |
|---|---|---|---|
| A. Indifferent cells, | | | BLASTOCYTES |
| B. Epithelial cells, | | | EPICYTES. |
| C. Connective tissue cells, | | | |
| Fibrous tissue cells, | FIBROCYTES. | DESMOCYTES. | MESOCYTES. |
| Cartilage cells, | CHONDROCYTES. | | |
| Bone cells, | OSTEOCYTES. | | |
| Fat cells, | LIPOCYTES. | | |
| etc. | etc. | | |
| D. Bone marrow cells, | MYELOCYTES. | | |
| Spleen pulp cells, | etc. | | |
| etc. | etc. | | |
| E. Free cells. | | | |
| Blood, Lymph, etc. | LEUCOCYTES. | ALETOCYTES.* | |
| | ERYTHROCYTES. | | |
| | LYMPHOCYTES. | | |
| F. Nerve cells, | | NEUROCYTES. | |
| G. Muscle cells, | | MYOCYTES. | |

* Αλήτης Wanderer.

The histiomata are named by adding the termination *-oma* to a root expressing the nature of the tissue which is characteristic of the tumour. The adoption of this rule involves the abandonment of the term *epithelioma* as expressing one of the kinds of carcinoma. In this sense the term is wholely unnecessary and redundant and implies a distinction from other kinds of carcinoma which is not warranted by the pathology of the disease. For the same reason the term *endothelioma* is discarded in the malignant sense. Owing to the term *epithelioma* having been used as implying malignancy the epithelial histioma are called *papillomata* when the epithelium covers the surface, and *adenomata* when the epithelium forms tubes and spaces imbedded in a connective tissue stroma.

### Relation of Tumour Growth to other processes.

There are numerous other diseases which bear a close resemblance to tumours in their general characters. They are characterised by the progressive nature of their course and by their apparently causeless origin.

In the breast we occasionally meet with a *progressive hypertrophy,* the whole breast enlarging without apparent cause and with no apparent limit to its growth. Similar cases are also met with in the thyroid (*Goitre*), in the prostate, etc.

Next we find cases in which one of the tissues of an organ, usually the connective-tissue, undergoes a progressive increase. This is seen in *progressive fibrosis* of nerves, in the prostate, and probably in some cases of cirrhosis of the liver.

The distinction between these conditions and histiomata is that in these conditions the whole organ is affected, the tissues retaining their typical relationship but being altered in amount, while a tumour is localised to one part of the organ. Progressive hypertrophy of, *e.g.*, a glandular organ corresponds to a diffuse adenoma while progressive fibrosis corresponds to a diffuse fibroma.

Again we find cases where the tissues undergo a *progressive atrophy,* as in the primary muscular atrophies, in progressive muscular atrophy, and in some other nervous diseases.

We also find cases of continued excess or defect of functional

activity (*Hyperergasis, Hypo-ergasis*) as, for example, in diabetes insipidus, diabetes mellitus, exophthalmic goitre, and numerous nervous and mental diseases.

Lastly we find cases of *progressive metaplasia* as seen in Myositis ossificans and probably in the articular cartilages in Rheumatoid arthritis.

Other examples of one or other of these conditions are found in pernicious anæmia, erythrocythæmia, leucocythæmia, Hodgkin's disease, etc.

The processes underlying these diseases have always been a puzzle to pathologists and clinicians. They are closely allied to tumour growth. Like tumours these diseases arise without apparent cause or many different causes may appear to give rise to the same disease. Like tumours, also, their course is progressive and only slightly, if at all, influenced by treatment, and recovery is rare.

We must, then, consider tumour growth as a member of a group of processes which together may be called the *progressive processes* as opposed to the *reactive processes* which are seen in the inflammatory and adaptive changes.

### Difference between Simple and Malignant Tumours.

A most important point in connection with the classification of tumours is the following:—Is it possible by a histological examination to say definitely whether a given tumour is malignant or not? I have said that it is possible to allot any given tumour a place in the classification provided that we are sure of what we see with the microscope. In certain cases, however, it is not always easy to say exactly what the structure is at which we are looking. Endothelial cells resemble epithelial cells or sometimes connective tissue cells very closely and certain inflammatory conditions resemble certain tumours. Also certain carcinomata bear a close resemblance to certain adenomata. This difficulty can often be overcome by examining a number of sections from different parts and prepared by different methods.

In order to answer the above practical question satisfactorily it is necessary to decide on the question—What do we mean

by malignancy in a tumour? The signs of malignancy are usually given as rapidity of growth, ulceration, infiltration, the production of metastases, and the presence of cachexia. To my mind the one necessary feature of malignancy is infiltration of the surrounding parts. The infiltration may be present in a very varying amount and may not be evident to the unaided eye but it can always be detected by the microscope if the right part of the tumour be examined. In other words, the distinction between the histiomata and the cytomata lies essentially in their mode of growth. If, for instance, we examine a chondroma we find everywhere typical cartilage surrounded by fibrous tissue (Fig. 3). In growing, it displaces the surrounding tissues without infiltrating them. In a chondro-sarcoma, on the other hand, the nodules of cartilage, instead of being surrounded by fibrous tissue, are surrounded by sarcoma cells, and these cells are able to infiltrate the surrounding tissues, proliferating there and giving rise to the cartilage as a secondary product (Fig. 4).

Again, an adenoma presents itself as an encapsulated or pedunculated tumour and the epithelium of the tumour is everywhere surrounded by some of the stroma (Fig. 5), whereas a carcinoma, while it may resemble an adenoma in its older parts (Fig. 6), yet, in its actively growing parts, shows epithelial cells penetrating the interstices of the surrounding tissues, and any tubes or spaces in the carcinoma are of secondary origin (Figs. 7, 8). The tubes, once formed, are capable of continued growth in which they retain their tubular character. Hence, to be certain of the diagnosis in a carcinoma, especially in the columnar celled type, it is necessary to examine the spreading margin. Here it may be remarked that tumours do not always grow uniformly; one part may grow for a time actively and then cease while another part takes on active growth. Hence it may not be easy to find the particular part of the tumour, the study of which will give a decided answer to the question of the presence or absence of malignancy.

In order, then, that the pathological diagnosis may be of value, the pathologist must always be supplied with as much of the tumour as is available, including, if possible, some of

the surrounding tissues, and he should be informed of the clinical features of the case. The use of the microscope affords the most certain, sometimes the only, means of diagnosing the nature of a tumour.

We can now reply to our question as follows :—Theoretically it is always possible by a histological examination to say whether a given tumour is malignant or not.

Practically it is possible in the great majority of cases to give a decided answer from a simple microscopical examination. In the few remaining cases it may be necessary to make an extended examination of different parts of the tumour before coming to a definite conclusion.

It is not always necessary to detect actual infiltration of the surrounding tissues to give a diagnosis of malignancy, as there are other factors which assist in the diagnosis, such as irregularity in the epithelium (in carcinoma), rapid and irregular proliferation as indicated by mitotic figures, etc., etc. It is often easier to say that a tumour is malignant than to give a decision on the less important question as to what type of cancer to refer it.

We see, then, that the cytomata differ from the histiomata in their mode of growth. In the former the spreading part is cellular, the formed tissues being of secondary formation, and in the latter the formed tissues grow as tissues from the first. In the former, the mode of growth is infiltrative, in the latter expansive. I shall have occasion to return to this point.

## Rudiment of Origin.

In considering the life-history of a tumour we have, first, to consider what is the rudiment from which the tumour springs? What is the first beginning of a tumour?

Cohnheim endeavoured to explain the origin of tumours by supposing that they originated from rudiments which were sequestrated in embryonic life from the surrounding tissues, and took no further part in normal development. He supposed that these rudiments, retaining their embryonic characters, would, when the surrounding conditions were altered, as, for example, by irritation, show a greater power of proliferation, and he thus

explained the great powers of growth exhibited by tumours. While this theory will not explain all tumours and is unnecessary in the great majority of tumours, it is applicable in certain cases.

Beard[3] attributes tumours to aberrant germ cells. According to this authority the fertilised ovum, in its initial proliferation, gives rise to a definite number of primitive germ cells, one of which gives rise to the embryo, while the others migrate into the body of the embryo and there become the primary germ cells of the sexual glands. Occasionally, instead of passing to the sex glands, these germ cells become deposited in other parts, where, in after life, they may give rise to tumours. There is not any evidence in support of this hypothesis, which is based on purely embryological grounds, and a strong objection to it is that it will not explain the close resemblance of a tumour to the tissues at its site of origin.

It was laid down in the definition of a tumour that the component parts of a tumour resemble structures normally found in the body. When we consider individual tumours we can expand this statement and say that the cells or tissues of which a tumour is composed resemble, in the great majority of cases, those present at the site in which the tumour originated. Seeing that this resemblance exists it is natural to suppose that the tumour arises, directly or indirectly, from the normal structures at the place of origin, and we can, I think, take it as a fact that this is the case in the great majority of tumours.

There are cases in which the tumours are composed of tissues not normally present at the site of origin, but even in these cases it is not always necessary to suppose an aberrant rudiment. We know, for instance, that under certain circumstances, it is possible for tissues to undergo metaplasia. The various kinds of connective tissue are interchangeable, as are also the various kinds of epithelium. We know, for example, that cartilage or bone may arise in connective-tissue: hence it is not necessary to suppose an aberrant rudiment of cartilage to explain the presence of a chondroma in positions in which no cartilage normally exists. Again, we know that columnar epithelium may undergo metaplasia into squamous; hence it is not necessary to suppose an aberrant rudiment to explain the occurrence of a squamous-

celled carcinoma in the body of the uterus. I have seen a carcinoma of the cæcum which to a large extent consisted of typical squamous cells.

Ribbert [7] accepts Cohnheim's views for many tumours, but in addition states that the rudiments from which tumours originate may arise during post-natal life. In this case they consist, not of the normal tissues directly, but of some portions sequestrated from them by an inflammatory process or otherwise separated from their organic connections with the neighbouring parts, and these rudiments, being freed from the normal influences of the surrounding tissues, proliferate and so give rise to tumour growth. The first change in carcinoma, for instance, is a kind of inflammatory change in the connective tissue which proliferates and penetrating between the epithelials cells isolates them. These cells, being thus isolated and freed from the influences of the neighbouring cells, proliferate, and thus give rise to the carcinoma.

This idea, while undoubtedly true in many cases, is not, I think, necessary for all cases. It is a point very difficult to prove, and in some cases the connection between the tumour and the normal tissue is so close as to make it difficult to believe that the former has not developed directly from the latter.

We can say, then, that tumours arise from normal tissues directly or indirectly. They may also, in certain cases, arise from rudiments such as those postulated by Cohnheim. We may add that one tumour may arise from the tissues of another tumour.

The rudiment from which a tumour grows may be of any size. Some may start from a single cell, while others may originate from a whole organ, as in cases of diffuse carcinosis of the breast, stomach, or liver.

## Mode of Growth.

The next point to consider is: How does the tumour grow from the rudiment? This question will be considered more fully later on. We may here state that tumours grow by proliferation of their own cells, the surrounding tissues taking no part in the process. We must, however, limit this statement

by saying that the area from which the tumour arises may increase in size, and, to this extent, the surrounding tissues may take some part in the growth, but it is only the tissues in direct continuity with the point of origin which act in this way. For instance, in a carcinoma of the breast the acini surrounding the tumour take no part in the growth, but are destroyed by it. Also in a carcinoma of the skin, while the area of origin may extend, yet the tumour itself grows by proliferation of its own cells, and, if it come in contact with the epidermis at a distance from the point of origin, the epidermis is destroyed by the advancing tumour and takes no part in the growth.

I have seen an angeioma of the liver which measured about 12 inches in diameter and reached as low as the iliac fossa hanging from the right lobe of the liver.[6] It was a cavernous angeioma and had been of rapid growth as far as could be determined from the history. Now throughout the tumour, even at its lowest margin, could be found, in the trabeculæ between the cavernous spaces, bile ducts and groups of hepatic cells (Fig. 9). The growth was too great to be due to a simple angeiectasis, *i.e.*, to a simple dilatation of pre-existing vessels, and, if the growth had proceeded by proliferation of the tumour cells alone we should not expect to find the hepatic remnants throughout it. Hence the most obvious explanation of the growth is that it started in a limited area, and, as growth proceeded, successive capillaries abutting on this area took on an active proliferation, and so the area of origin continued to extend among the liver cells, and, in consequence, the bile ducts and other hepatic remnants became elongated with the growth of the tumour.

Centripetal growth, then, does not occur except in connection with the area of origin, but the growth is centrifugal.

Centrifugal growth may be either central (expansive), occurring in the substance of the mass, or peripheral (infiltrating), occurring at the periphery. The former is the mode of growth characteristic of the histiomata, the latter of the cytomata. Peripheral growth, however, is usually accompanied by central or expansive growth, but in some cases the periphery may continue to grow while the centre has ceased growing or has become necrotic.

# Part II.

# CANCER

## PART II. CANCER.

### CYTOMATA.

Coming now to the cytomata with which we are more particularly concerned, you will observe that I have divided this class of tumours into three genera, *Blastocytomata, Sarcomata,* and *Carcinomata,* and I must define what I mean by these three kinds of cancer.

When a fertilised ovum divides, the cells which first result from its division are indifferent cells or *Blastocytes; i.e.,* they are cells which show no differences by which they can be distinguished from one another and, in the course of development, each may give rise to more than one kind of cell. As proliferation proceeds these cells become differentiated and, when this takes place, we can distinguish two types of cell :—*Epicytes,* or cells arranged in contact with each other forming a membrane which covers a surface or lines tubes and spaces (epithelial cells), and *Mesocytes,* which are cells separated from each other by intercellular substance or by the intervention of more or less definite fibrillar tissue (connective tissue cells, muscle and nerve cells). To these three types of cells correspond the three genera of the cytomata.

BLASTOCYTOMATA.* A blastocytoma is a tumour of which the essential cells are indifferent cells or *blastocytes.* The only means by which we can recognise these cells is the fact that they become differentiated into different types of cells, both epicytes and mesocytes. Hence the blastocytomata are mixed tumours containing epithelial and other elements both derived by differentiation from the fundamental indifferent cells. The best example of this kind of tumour is seen in the congenital mixed tumour of the kidney which is the commonest form of renal growth in children. If we study one of these tumours carefully we find that the most conspicuous elements are small

* In the Erasmus Wilson lectures (10) I named these tumours BLASTOMATA. I have altered the name because objection has been taken to the use of the term Blastoma in this sense, this term having been previously used to include all tumours.

round cells resembling sarcoma cells (Fig. 10). Embedded in these are numerous epithelial tubes and, here and there, can be found striated and smooth muscle fibres and the various forms of connective tissue. Now a careful examination reveals the fact that, in places, there is direct continuity between the round cells and the epithelial cells and it can be determined that the epicytes arise from the small round cells. The earliest stage in the process is seen as a circular grouping of some of the round cells (Fig. 11). Later on these cells assume the characters of epithelial cells and the centre of the group disappears leaving a lumen to the epithelial tube thus arising (Fig. 12), but still there is no sharp demarcation between the epicytes and the surrounding cells. The tube, once formed, continues to grow and develops a basement membrane. Hence, in many places, the epithelial tubes appear to be sharply marked off from the surrounding cells and to have no immediate connection with them. It is only in certain places that the connection can be traced. In other places a similar connection can be traced between the fundamental cells and the various other forms of tissue present (Fig. 13). In support of this view of these peculiar tumours is the fact that the epithelial tubes, while often showing branching, are independent of each other and lie free among the surrounding fundamental cells. This can be determined by means of serial sections.

In the later history of these epithelial tubes it will sometimes be found that the wall becomes invaginated on one side and the epithelial cells become flattened so that a structure is produced which bears a striking resemblance to a glomerulus before any blood-vessels have penetrated into it (Fig. 14).

Another example of the blastocytomata is to be found in the mixed tumours of the parotid. In these tumours the fundamental cells are polygonal cells with branches which communicate with the processes of neighbouring cells. If we examine the preparation closely we find that, on the one hand, by approximation of the cells we get epithelial cells—the processes becoming prickles—and, on the other hand, by a separation of the fundamental cells by the intervention of a mucoid intercellular substance we obtain mucous tissue which in its turn may give rise to cartilage or fibrous tissue (Fig. 15).

Tumours with similar characters are found in the testis, the brain, and other situations.

It seems clear that in these tumours differentiation proceeds with proliferation and that the fundamental cells are indifferent cells, being capable of giving rise to various forms of differentiated cells. Hence the rudiment of origin of these tumours is a group of undifferentiated cells which retain their capacity for undergoing differentiation until the tumour develops. This is a rudiment in Cohnheim's sense. In the case of the blastocytoma of the kidney the rudiment would consist of the cells of the paraxial mesoblast which give rise to the intermediate cell mass from which the Wolffian body is developed and the development of the tubes in the tumour corresponds exactly to the development of the tubes in the Wolffian body and to the development of the glomeruli and convoluted tubes of the kidney which are of mesoblastic origin. The presence of striated muscle is accounted for by the close association of the intermediate cell mass with the mesoblastic somites from which the muscles are developed.

Sarcomata. I have divided the sarcomata into two groups —the pure and the compound.

A pure sarcoma consists of cells and intercellular substance alone without the presence of any formed tissues, whereas the mixed forms contain one or more forms of definite connective-tissue in addition to the purely cellular portions, but these tissues are of secondary formation, being developed from the fundamental cells (Fig. 4). The pure sarcomata are subdivided according to the kind of cell present and the compound according to the different kinds of connective-tissue which are developed in them.

Carcinomata. The carcinomata, like the sarcomata, are subdivided according to the type of cell present, and we may, also, if we please, divide them into *pure carcinomata* in which no definite epithelium is present, the cells being arranged irregularly, and the *compound carcinomata—adenocarcinoma* or *papillocarcinoma*—in which definite epithelium is formed either lining spaces or covering outgrowths.

It will be observed that I include the malignant endothelial

tumours among the carcinomata. I do this because endocytes bear a close resemblance to epicytes both in structure and arrangement, in fact endocytes are only a particular species of epicytes. We find that, both developmentally and under pathological conditions, epithelial cells may assume an endothelial character, and that endothelial cells may assume the columnar, cubical, or squamous type. Hence tumours arising from endothelium often bear a close resemblance to the columnar (Fig. 16), spheroidal (Fig. 17), and squamous-celled carcinomata (Fig. 18).

We see, then, that the three genera of the cytomata have similar characteristics. In all of them the fundamental elements are cells and in all of them tissues may arise as secondary formations. The pure blastocytoma, *i.e.*, a tumour composed entirely of blastocytes, probably exists, but we have no means of recognising a blastocyte apart from the differentiated cells which arise from it. Possibly the tumour which we know as the round-celled sarcoma is an example of a pure blastocytoma. The pure Carcinomata, *i.e.*, the carcinomata in which the epicytes are arranged irregularly without any tendency to form definite epithelium are seen, especially in the spheroidal-celled and in some sqamous-celled growths, and the pure sarcomata are the ordinary round-celled, spindle-celled and giant-celled sarcomata.

In the compound cytomata we recognise, in the blastocytomata, epithelium and connective-tissue, muscle, etc.; in the sarcomata various forms of connective-tissue; and in the carcinomata definite epithelium, either in the form of tubes (*adenocarcinoma*) or as papillary outgrowths (*papillocarcinoma*).

## Cancer in Animals.*

Cancers and other tumours occur in all kinds of vertebrate animals and probably in some invertebrates (Figs. 19—24). They resemble in structure and characters the corresponding tumours in Man, and much valuable knowledge has been gained

* For an account of cancer in animals see the various Scientific Reports of the Imperial Cancer Research Fund.

from the experimental study of these tumours. This experimental study has been carried on especially in mice which are comparatively frequently affected by tumours and it has been found possible to transplant from mouse to mouse carcinomata, sarcomata, and chondromata so that the growth of the transplanted tumours can be followed from the earliest beginning. It is found that the tumour originating in a mouse as the result of inoculation with a small portion of a tumour from another mouse is the result of the proliferation of the cells of the portion of tumour introduced.

### Rudiment of Origin.

With regard to the rudiment of origin of a cancer there is little to add to what we have already said in regard to tumours in general. Cancers may start from the normal tissues of the part, or from sequestrated rudiments, or again from other tumours, and the rudiment may be single or multiple. In certain cases a carcinoma may start from the epithelial cells of a whole organ. These are, perhaps, more correctly described as cases of diffuse *carcinosis* of the organ. Such cases have been described in the breast and stomach and occasionally in the liver and other organs. Primary carcinoma of the serous membranes, particularly of the pleura, usually takes this form, appearing as a general thickening of the membrane involved. The same may be the case in sarcomata, *e.g.*, in diffuse sarcoma of the liver. These conditions bear the same relation to Carcinoma and Sarcoma that progressive fibrosis does to Fibroma.

The area of origin of a carcinoma may, in some cases, increase in size, successive neighbouring portions of epithelium taking on a cancerous growth, but, as a rule, the increase in size, *e.g.*, of a cancerous ulcer, is due to continuous proliferation of the cells arising from the original rudiment, the surrounding epithelium being destroyed and taking no part in the tumour growth. Hence, from an examination of the tissues in the neighbourhood of a cancer, we cannot draw any conclusions as to the structures from which it has arisen.

As to the organs from which cancers arise we can say that the organs most frequently affected are those which are exposed

to chronic irritation or traumatism or those which are liable to considerable variations in functional activity.

## Mode of Growth.

A cancer, like other tumours, grows by proliferation of its own cells. The predominant type of growth is, as we have seen, peripheral; that is to say, the tumour cells at the periphery proliferate and penetrate the surrounding tissues thus giving rise to the infiltration which is the characteristic feature of malignancy. In most cases, however, this peripheral growth is associated with central expansive growth, *i.e.*, it is not only the younger peripheral cells which proliferate but also the older cells in the mass of the tumour.

When this expansive growth occurs to a considerable extent the tumour may present an appearance of encapsulation due to the compression and consolidation of the surrounding tissues by the expanding mass. The encapsulation is, however, apparent only, and examination with the microscope will show that the peripheral cells are proliferating beyond the apparent capsule and infiltrating tissues. This apparent encapsulation is more frequent in Sarcoma than in Carcinoma while in Carcinoma more frequently than in Sarcoma we see the opposite condition, the peripheral cells proliferating and infiltrating while the central cells have lost their power of proliferation and are degenerating. Hence a carcinoma, as is seen sometimes in Rodent Ulcer, may continue to spread while the older parts become healed.

The peripheral mode of growth explains the destructive characters of cancers. The cells penetrating the surrounding tissues, find their way into all available spaces and proliferating there separate the constituents of the tissues and cause them to undergo atrophy *in situ* without displacing them (Fig. 25). Cancer cells can penetrate into and proliferate within fat cells (Fig. 26) and striated muscle fibres. Dense substances such as cartilage, in which there are no available channels, withstand the encroachments of a cancer for a long time. We can say, then, that cancers replace, rather than displace, the surrounding tissues.

## Modes of Extension.

Permeation. Cancer spreads to the parts surrounding the primary mass by a mode of extension known as *Permeation*. We have seen that the primary mass grows by the peripheral cells proliferating and infiltrating the surrounding tissues. Permeation is an extension of this process, the cells proliferating continuously along the lymphatic channels. In the case of external cancer this permeation of lymphatics takes place to a greater extent in the deep fascia than in the superjacent or subjacent tissues while here and there processes of the growth grow towards the surface and give rise to nodules of tumour having no apparent connection with the primary mass. Thus are explained the cutaneous nodules sometimes seen in Carcinoma of the breast and also the infiltration of bones, muscles, etc.[4] This permeation is not confined to the lymphatic channels but may take place along veins, tendon sheaths, nerve sheaths, ducts, etc., any natural channel forming a path by which the cancer can grow. While this proliferation takes place in continuity we may find that the chain of cells is not continuous at any one moment. While the cells at the extremity of the chain are proliferating, some of the cells nearer the primary mass may have disappeared and the channel been obliterated by cicatrisation. The direction of growth in permeation is not dependent on the direction of the current in the lymphatics, etc., but takes place to an approximately equal extent in all directions radiating from the primary mass. Secondary tumours may also be centres of permeation.

Growth of the same kind, viz., proliferation in continuity, may take place over long distances. We may find a tumour growing along the large veins or along the whole length of the thoracic duct.

Metastasis. When the growth has penetrated into a lymphatic or vein it is easy to understand how individual cells or groups of cells may become detached and carried on by the lymph or blood-stream. Such detached cells, being carried to the smaller arteries or capillaries, become lodged as emboli and commence to proliferate, thus giving rise to a new tumour with

no direct communication with the primary growth. This phenomenon is known as *metastasis* and the growth as *metastatic growths*. The lymph glands, lungs and liver are naturally, owing to their position with regard to the circulation, the most frequent seats of metastatic growths. The entry of the cancer cells into the blood-vessels may be either directly, by penetrating the wall of a capillary or vein (Fig. 27), or indirectly by way of the lymphatics.

Certain organs, such as the alimentary canal and muscles, are very seldom the seat of metastatic growths. These organs may escape when there is widespread metastasis in other organs, and we must suppose that the tumour cells in these cases are carried to the alimentary canal and muscles as well as to the other organs. Apparently, however, the tumour cells in these situations do not meet with the conditions which are necessary for proliferation, and are therefore destroyed or remain latent.

Independent secondary growths may also arise from cancer cells being conveyed along the lumen of a canal, such as the alimentary canal or a duct, and settling in new situations. They may also follow upon the dissemination of cancer cells in the serous cavities.

Metastatic cancers do not usually show such an extreme power of infiltration as do the primary tumours. Often they are apparently sharply circumscribed and appear to be encapsulated. This is largely due to the fact that the expansive growth takes a larger share in the enlargement of the tumour than the peripheral, and hence the surrounding tissues are displaced rather than infiltrated.

Occasionally metastasis has been described in a tumour which does not show malignant characters histologically. Thus chondromata have been described as giving rise to metastases. In the great majority of these cases careful examination shows that the tumour is not a simple chondroma, but is a chondro-sarcoma or a carcinoma with a cartilaginous stroma. Apparently, however, there are cases where this explanation will not apply and where the tumour is a pure chondroma and does not show infiltration. These cases are characterised by a distinct growth of the tumour along the veins, and, given the

presence of a growing tumour in the lumen of a vein, it is not difficult to understand how portions can become detached and so form emboli. The presence of the chondroma within the vein is due to the tumour having come in contact with the vein from outside; ulceration of the vein, due to the pressure of the unyielding cartilage, then occurs, allowing the tumour to grow into the lumen of the vein. These cases are, however, excessively rare.

## Multiple Tumours.

Multiple tumours are not as rare as they were once thought to be. The different tumours may be all of the same nature or may be of different types. They may be all malignant or all non-malignant or some may be malignant and others simple. Also the different tumours may arise in the same or in different organs and may even be combined into one growth.

I have, myself, seen several cases of multiple cancers. One of them was of particular interest. It was a case where a man had his eye removed for a melanotic sarcoma. Two years later he died with a large mass of growth in one of his ribs. Naturally this was supposed to be a metastatic growth but it proved to be a squamous-celled carcinoma apparently of endothelial origin, seeing that no primary tumour of this kind existed anywhere else in the body (Fig. 18). Besides this tumour he had innumerable spindle-celled sarcomata in the liver, each tumour being about the size of a pea and none of them pigmented.

Another interesting case was a columnar-celled carcinoma of the stomach in which the stroma was sarcomatous, being composed of small round cells. In this case there were several metastatic tumours all of which were sarcomatous. This appears to have been a case of primary carcinoma, in the stroma of which a sarcoma developed, the sarcoma becoming predominant.

Cases have also been described of mixed carcinoma and sarcoma in which the metastases have been some of one type and some of the other.

## The Stroma of Carcinoma.

A carcinoma is usually described as consisting of epithelial cells in a connective-tissue stroma, and the question arises whether both constituents are to be regarded as integral portions of the tumour. There can be no doubt that it is the epicytes which are the active constituents of the tumour, and the fibrous tissue is merely a supporting tissue derived from the connective-tissue of the organ in which the tumour is growing. The growing part of a carcinoma is entirely cellular, the epicytes infiltrating the surrounding structures (Figs. 25, 26), and the stroma is produced as a secondary formation from these structures by condensation and proliferation of the connective-tissue. This fact has been confirmed by the observation of experimental carcinomata in mice. In every case in which a carcinoma is transplanted from mouse to mouse the stroma degenerates, while the epicytes continue to live and proliferate. A new stroma is subsequently supplied by proliferation from the tissues of the animal into which the tumour has been transplanted.[2] There are cases, however, which it is difficult to explain on this view that the stroma is formed from the tissues in which the tumour is growing. Such are the rare cases of carcinoma with a cartilaginous stroma which gives rise to metastatic tumours of the same character. In some of these cases, at any rate, the tumour grows along the interior of a vein, and a portion may be bodily detached containing both epithelial cells and cartilage, both of which continue to grow when they become lodged in a new situation. We should have to assume in this case that the tumour was a combined tumour.

Whether this is so or not there is no doubt that the epicytes have an influence on the stroma and that the cells which give rise to a metastasis can so influence the tissues at the new site that they produce a stroma with the characteristics of the stroma of the original tumour. A carcinoma arising in any organ usually shows a stroma resembling the stroma normally present in that organ and the metastases show a similar stroma. This is especially seen in adrenal tumours. In the transplantation

of mouse carcinoma the new formed stroma assumes the characters of the stroma of the original tumour.

I have mentioned that a sarcoma may arise in the stroma of a carcinoma and it has been observed in the experimental transplantation of carcinomata in mice that occasionally, during successive transplantations, a sarcomatous stroma appears and eventually supplants the carcinoma, the sarcoma itself being transplantable.

## Vascular Supply.

The blood-vessels in a cancer are derived from the capillaries of the part in which the cancer originates. As the tumour grows the capillaries enlarge and lengthen and new capillaries may be formed from them. At the same time the gradually enlarging tumour engulfs more and more of the surrounding capillaries and other vessels which then become available for its nutrition. The blood-vessels in a cancer retain the capillary structure to a large extent although they may become dilated into sinuses and they show little tendency to become fully developed into arteries and veins. Hence the vascular system of a cancer consists mainly of capillaries and wider sinus-like channels arranged in an irregular network which connect with the blood-vessels of the surrounding part at all points in the surface of the tumour.

In a carcinoma the blood vessels run in the stroma. In those cases of Carcinoma in which the stroma is present in very small quantities and in sarcomata where the vessels run along the cells, hæmorrhages are likely to occur owing to the imperfect structure of the blood-vessels. In endothelial cancers the tumour cells themselves may form new blood-vessels in the same way that the cells of a columnar-celled carcinoma may form epithelial tubes.

## Ultimate Destination.

Having considered the sources and modes of growth and extension of cancers we have next to consider what is the ultimate destination.

Unfortunately, the great majority of cancers continue to

increase until death results. We have seen, however, that some cancers while spreading in one part heal in others. These cases are seen especially in Rodent Ulcer and atrophic Schirrus. Such tumours may continue to grow for years without producing any except local effects.

Some tumours, even sarcomata and carcinomata, disappear spontaneously. Several cases of undoubted cancer verified by histological examination have been described which have disappeared completely, either without any treatment, or with such treatment as could not produce such an effect of itself. We do not in the least know what are the conditions which lead to such a result. We do not know whether there is a spontaneous cessation of proliferation or whether there is an enhanced effort on the part of the organism to stop the encroachment of the tumour. From the rarity of these cases it would seem to be an idiosyncrasy on the part of the individual tumour or patient and we have no means at present of reproducing the conditions in other tumours or other patients.

Some light, however, has been recently thrown on this question by the experimental investigation of mouse cancer. It is not uncommon for a cancer in a mouse, after growing for some time, to cease growing and to degenerate, ultimately disappearing completely. Such mice are found to be immune to subsequent inoculation. This immunity is specific in the sense that a carcinoma does not confer immunity towards a sarcoma and *vice versa,* and it is specific in a stricter sense. It is found that a given carcinoma confers a much higher degree of immunity towards subsequent inoculation of the same tumour than towards a carcinoma of different origin.

### Degenerative Processes.

Apart from disappearance, cancers may undergo various retrogressive processes, such as fatty and colloid degeneration and calcification. These changes in cancers are not always to be regarded as strictly degenerative changes. We find that the alterations often correspond to the changes which take place normally in the cells from which the cancer has arisen, and the changes are thus more allied to secretory than to degenerative processes. Fatty changes are especially common in breast

cancers; the cells of a carcinoma of the thyroid secrete colloid; columnar-celled carcinomata of the stomach and intestines secrete mucin; those of adrenal carcinomata contain fat and cholesterin. Also sarcomata of bones are prone to ossify or calcify.

Cancers can also exhibit inflammatory changes.

## Metabolism.

We know little about metabolism in Cancer. Seeing that the cancer cell is derived from the cells of the organism we should naturally expect that, making allowance for the rapid proliferation, the metabolism would be similar to that of the normal tissues of origin. I have mentioned that carcinoma cells often secrete the same substances as the normal cells of the organ in which the carcinoma arises. Besides the examples given above I may mention that trypsin has been found in carcinomata of the pancreas and pepsin in carcinomata of the stomach.

Many carcinomata contain a large amount of glycogen, and some have maintained that the amount of glycogen is proportional to the degree of malignancy. This is, however, not necessarily the case. While it is common in cancers, it is also found in some simple tumours, being always present in chondromata. The presence or absence of glycogen appears to depend more on the origin of the tumour than on the rapidity of its growth.

There do not seem to be any definite changes in the urine, temperature, pulse etc., due to cancer *per se*.

In studying questions of metabolism it is difficult to separate the effects of the cancer *per se* from those due to the disturbance of the organ affected.

## Clinical Features.

The clinical features of cancer can be explained by the pathology of the disease. The fixation of the tumour to the surrounding parts is explained by the infiltrative mode of growth. The appearance of cutaneous nodules in the neighhourhood of an external cancer is attributable to the permeation

of the lymphatics. The extension to the lymphatic glands is attributable to permeation and embolism, and visceral deposits depend on metastasis by the blood-stream. Degeneration and softening depend on the imperfect blood supply, and cachexia on the drain of nutrient material combined with the absorption of the products of disintegration of the tumour cells, and of bacterial products in the case of ulcerated cancers. There does not seem to be a specific cancer toxin.

Recurrence after removal is due to imperfect removal, and is not characteristic of cancer alone. Simple tumours recur if the removal is incomplete. In cancer, however, since the tumour is not encapsulated, it is impossible to define its bounds, and hence outlying cancer cells are very liable to be left behind to give rise to a recurrent growth. Also, since cancer cells are transplantable, infection of the wound is liable to occur at the operation. When recurrence occurs at a distance from the original operation it is not necessarily to be attributed to imperfect operation. We have seen that multiple tumours are not so very uncommon; hence when recurrence takes place at a distance it is quite likely that the new tumour is independent altogether of the original one. This is especially likely to be the case when the new tumour arises in a part which is a common site of a primary tumour. When, for instance, after removal of a breast, a cancer appears in the other breast, it is possible, and even probable, that this second tumour is a new formation altogether and independent of the former one. The breast is a rare situation for a secondary tumour, while it is a common site of primary growths. In some of these cases of recurrence after operation the new tumour shows a different histological structure from the original one, and hence must be regarded as independent.

## Part III.

# CAUSATION

# PART III. CAUSATION.

## CAUSAL FACTORS.

HAVING considered the rudiment of origin and the mode of growth by which the cancer or other tumour grows from the rudiment, we have next to consider why tumour growth occurs or, in other words, what is the cause of Cancer?

The causal factors which give rise to any disease can be divided into the *essential* causal factors, or those factors without which the disease in question could not arise, and the *adjuvant* causal factors, or those factors which assist in the causation of the disease without being, themselves, individually necessary. Causal factors may also be divided into the *extrinsic* and *intrinsic* factors.

We have, then, two classes of diseases:—(1) Those in which the essential causal factors are extrinsic; (2) those in which the essential causal factors are intrinsic. A disease may be specific in two ways:—(*a*) It may be characterised by a specific extrinsic causal agent; (*b*) it may be characterised by specific lesions. If we consider a disease as characterised by a specific extrinsic causal agent we find that it does not show constant lesions. If, on the other hand, the disease is characterised by specific lesions it is not characterised by a specific extrinsic causal agent.[14] In other words, any extrinsic causal agent will, under differing circumstances, give rise to different lesions, and any

of their enemies, and, in the course of evolution, it has come about that those organisms which are most liable to destruction have developed the greatest proliferative capacity, as in the case of bacteria, animal parasites, fish, etc.

Now what is true of living organisms in general is equally true of the constituent parts of the organism, that is, of the cells which make up the structure of the organism.

We find that all the cells of the organism are capable of proliferation in a varying degree. All proliferate during the development and growth of the organism. After a certain time, which differs in different organs, we find that some cells, such as neurocytes, have practically lost the power of proliferation; others, such as myocytes and desmocytes, retain the power of proliferation under certain conditions, while some epicytes and the mother cells of leucocytes and erythrocytes continue to proliferate throughout life to make good the loss due to various causes. Ova and spermatozoa lose the power of proliferation on attaining maturity, to regain it only by subsequent fertilisation.

Now the sites of origin of tumours correspond accurately to these facts. We find that neurocytes which have lost the power of normal proliferation only give rise to tumours with the greatest rarity; striated myocytes also extremely rarely give rise to tumours, while tumours arise from smooth myocytes much more frequently, and especially in parts in which, like the uterus, they show a physiological multiplication at intervals throughout life. The cells which most frequently give rise to tumours are the epicytes, and here again the most frequent sites are those where proliferation occurs regularly, or at intervals, throughout life such as the skin, alimentary canal, breast, and female organs of generation, while those epicytes which are normally more quiescent, as in the liver, kidneys, sweat glands, etc., only rarely give rise to tumour formation.

Proliferation, then, is an inherent property of the cell, as it is of the living organism, and those cells which have the greatest proliferative capacity are the most frequent sources of tumour growth. These facts tell strongly against the theory of embryonic rudiments as an explanation of tumour growth.

### Influences which Limit Proliferation.

We have next to consider why tumour growth does not occur as a general rule, or, in other words, what are the influences which limit proliferation under normal conditions? This is another way of stating the question, What are the influences which determine the form and size of any living being?

When the ovum undergoes segmentation the cells at first formed resemble one another. Soon, however, differentiation takes place and the cells assume characters which distinguish them from each other.

The different characters which the cells then assume appear to depend to a large extent on their position in the embryo, or, in other words, on their position in relation to the other cells of the embryo. Since the fertilised ovum contains all the potentialities of the organism, differentiation would appear to consist in the progressive loss or latency of certain characters and a consequent predominance of the characters which remain. Differentiation is found to a certain extent in some of the colony-forming protozoa in which some of the individuals have motile functions, others nutritive, others generative.

The cells, in spite of differentiation, retain their power of proliferation which is inherent in them, but different kinds of cells retain this power in very varying degrees.

### Co-ordinating Mechanism of the Organism.

Seeing, then, that this differentiation and proliferation occur in the different tissues, we have to ask ourselves, What is the co-ordinating mechanism of the organism? What are the influences which so regulate differentiation and proliferation that a perfect condition of equilibrium is maintained? Even in those cells which proliferate continuously there is a condition of equilibrium, because the proliferation is just sufficient to balance the corresponding destruction. In the skin and mucous membrane the epicytes proliferate only to such an extent as to replace the continual waste of cells which are cast off at the surface, and in the case of leucocytes and erythrocytes the production of new cells is balanced by the destruction which

takes place in the spleen and elsewhere. In those tissues, the cells of which do not show continuous proliferation, we find that the destruction of some cells is followed by regenerative proliferation of the cells which remain, which ceases when the defect is made good.

This question of the co-ordinating mechanism of the organism is the fundamental question for the pathology of tumours. If we knew what are the influences at work in producing the co-ordination, then we should be very near solving the problem of the causation of tumours, since tumours arise from a defect in co-ordination. Unfortunately we do not know what these influences are.

The form of any organism, which depends on differentiation and proliferation, is an inherent property of the species and is transmitted by heredity. Hence the co-ordinating influences are a property of the germ plasm and are transmitted equally by the ovum and spermatozoon. The influences within the organism are apparently intercellular, each cell exerting certain influences upon its neighbours. That such intercellular influences exist is shown by the co-ordination of the movements of the cilia in ciliated epithelium. This ciliary movement remains regular and co-ordinated in a detached piece of ciliated epithelium for a long time. As to the paths by which these influences pass from cell to cell, it would appear to be by direct continuity between the cytoplasm of adjoining cells, each cell being in protoplasmic continuity with its neighbours. This has not been entirely proved, but we can see the connections between the prickle cells of the epidermis, and they have been demonstrated in other kinds of epithelium, in smooth muscle, in bone, in fibrous tissue, and, according to some, they are present in cartilage.

In fact we have come to take too strict a view of cellular pathology. We are accustomed to explain all pathological changes by cellular activities without considering the organism of which the cells are the constituent parts. A living organism, however, is not a mere aggregation of cells, it is a distinct entity in itself—an individual—and the cellular activities are everywhere subordinated to the control of the whole organism.

The multicellular organism can be regarded as being composed of cells, differing in structure according to the function they have to perform, which everywhere retain intercellular protoplasmic connections, and it is through these connections that the co-ordinating mechanism of the organism acts. Development and growth are to be considered as primary properties of the organism as a whole, the proliferation of the cells being subsidiary. That is to say, the organism does not grow because the cells proliferate, but the cells proliferate because the organism grows.

Under normal conditions cells and tissues separated from their organic connections can form secondary connections with the neighbouring parts. Thus, when leucocytes penetrate between prickle cells, the intercellular bridges which they break in their progress are reunited behind them. Also in skin grafting and the reunion of wounds connections are formed with the neighbouring parts, and by means of these secondary connections the organism is again able to exert its co-ordinating influence and so to limit the cellular proliferation to the amount necessary to repair the deficiency.

The intercellular influences, besides regulating proliferation, also play a part in controlling functional activity.

While this co-ordinating influence is thus a property of the organism as a whole, it does not appear to be centred in any particular situation. It is also shown during the survival of detached portions, especially in the lower organisms. Hence a portion of one of the lower organisms can reproduce the whole, a heart removed from the body will continue to beat rhythmically, a fragment of ciliated epithelium still shows co-ordination of the ciliary movement.

### The Relation of the Tumour to the Organism.

e.g. [illegible]

If a portion of tissue, or group of tissues, be separated from its organic connection with the neighbouring parts, while retaining its position in the organism, and be unable to form secondary connections, it will no longer be subject to the control of the organism. Therefore, if it begin to grow, it will grow as an independent individual, dependent on the organism only as far

as its blood supply is concerned, thus forming a tissue tumour. Growing as an individual it will displace the surrounding tissues as it increases in size but, having no reproductive mechanism, it will not give rise to secondary tumours. If, however, a piece of the tumour be detached, as in the rupture of a papilliferous ovarian cyst or in a piece left behind in incomplete removal, such a detached portion will itself grow into a tumour resembling the old one provided that the vascular connections remain sufficient. While the tissues of which a simple tumour is composed are removed from the influences of the organism, they retain their connections *inter se* so that the whole tumour grows as an individual.

A simple tumour can thus be regarded as an asexually produced descendant which lives parasitically in the parent organism.

In a cancer the case is different. Here it is a cell which is freed from the co-ordinating influences of the organism. The cell thus proliferates, giving rise to new cells which are also independent. These cells penetrate into the spaces of the surrounding tissues, and wherever they settle they give rise to new groups of cells. A cancer, then, cannot be regarded as an individual; it is a colony of cells and the cells themselves are individuals.

The objection may, perhaps, be raised in this connection that the blood corpuscles of the normal body are independent cells and yet do not show the proliferative capacity which we find in cancer cells. The blood cells, however, are in no sense tissue cells. They are cells which, when they have become free, are destined for a limited existence only and do not proliferate under normal circumstances, except to a slight degree by amitosis.

A simple tumour, then, is to be regarded as an asexual multicellular organism while a cancer is comparable to a colony of unicellular organisms, and, just as unicellular organisms can form among themselves secondary associations with definite characters, as is seen in bacteria and the colony-forming protozoa and diatoms, so the cancer cells can form secondary associations *inter se* with the formation of distinct tissues. We find that

those cancers in which these secondary associations are formed most readily are the least malignant and *vice versa,* those cancers in which the cells remain independent of each other are the most malignant. For instance, among carcinomata the cells of the columnar-celled type most readily form tissues (epithelial tubes) and this is the least malignant species. On the other hand the cells of a spheroidal-celled carcinoma show very little tendency to form associations *inter se* and we find that the spheroidal-celled carcinoma is the most malignant form.

Another character in which cancer cells resemble protozoa is the limitless capacity for proliferation which they exhibit. Jensen's mouse cancer has now been growing for over seven years, that is, for a far longer period than the duration of life in a mouse, and it shows no sign of diminishing in vigour. It has been transplanted into innumerable generations of animals, and descendants of the original tumour are now to be found in laboratories throughout the world. At each successive transplantation the epithelial cells of the implanted tumour continue to proliferate and so give rise to the new tumour, so that the cancer cells show the same limitless proliferative capacity that is found in unicellular organisms.

Whether or not cancer cells show a still closer resemblance to unicellular organisms by occasionally manifesting a sexual process in the course of reproduction is not certainly known, but various observations on the characters of the mitoses in cancers tend to show that such is the case although some of the changes seem open to doubt. Appearances are sometimes found which suggest that cancer cells sometimes conjugate.[2]

Cancer cells show a further resemblance to unicellular organisms in that they will withstand the effects of cold. The cells of a mouse cancer can be kept at a temperature of 0°C. for several days or weeks,[2] and will even withstand the temperature of liquid air for some time and still retain the power of giving rise to a tumour when introduced into a new mouse,[8] [1] whereas if kept outside the living body at body temperature they quickly die.

A malignant tumour, then, is not a distinct entity in itself,

it is a colony of cells, and Cancer can truly be regarded as a process of infection by cancer cells.

The growth of a cancer thus differs from the growth of the organism. In the organism the proliferation of the cells is secondary to the growth of the whole cell-complex, while in a cancer the growth of the whole is the result of the proliferation of the cell units.

If Cancer be regarded in this light all the phenomena of malignant disease are easily understood.

### The Nature of the Intercellular Influences.

I do not intend to discuss here the phenomena of mitosis but I may remind you that cell division is initiated and effected by the centrosome with its associated amphiaster. These structures are formed of a substance known as *archoplasm*. It is not certainly known whether the archoplasm is a permanent constituent of the cell or whether it is modified cytoplasm, but there are reasons for believing that it is permanent and that the centrosome and archoplasm are handed down from cell to cell in the same way as the nucleus and cytoplasm. The centrosome appears to control not only the movements which result in cell division, but also amœboid and ciliary movements. Thus, while the nucleus and cytoplasm are concerned with nutritive and metabolic changes, the centrosome and archoplasm are concerned in the movements and division of the cell. It may be, then, that the intercellular connections are composed of archoplasm.

As to the nature of the influences which pass from cell to cell we know nothing. We can only say that they are an inherent property of the species and are handed down from generation to generation by heredity. They are present and active from the first commencement of division of the fertilised ovum, and hence cannot depend altogether on the presence of substances which are elaborated in organs which are developed at a later period, unless a store of such substance is laid up in the ovum sufficient to control development and growth in the early stages.

While it may be that some chemical substance, by reason of its chemical or physical properties, may play a part in controlling

cell proliferation, it is difficult to imagine how such a substance could control the form and arrangement assumed by the mass of cells resulting from the proliferation. It is inconceivable that the form of any species of organism can be dependent on the presence of any chemical substance. The controlling influences would seem to be of a more subtle nature. It is in connection with questions like this that we seem bound to admit the existence of a special form of energy which is peculiar to living organisms.

Chemical substances may, however, play some part in the control of growth, just as they take part in co-ordinating function in certain parts of the body. Indeed it is known that the secretions of the ductless glands have some influence on growth.

I have lately been investigating the nature and significance of certain crystals which occur in tumours. If a section of a cancer, which has not been subjected to alcohol, be examined by polarised light, crystals are found in nearly every case. Some of these crystals are fats or fatty acids and others are cholesterin. In addition there are minute needle-shaped or prismatic crystals occurring singly or in clusters, either in or among the cells. These crystals are distinguished by their peculiar behaviour on melting and subsequent cooling. Under these conditions they do not again solidify but assume a crystalline fluid condition appearing as doubly refracting globules (Fig. 28). These crystals are found especially in and among the healthy proliferating cells of the tumour while the crystals of fat and cholesterin are found especially in the degenerated areas. Degenerated areas are, however, often free from crystals of any sort while the proliferating areas may contain numbers of them.[12]

Having found these crystals in a number of cancers and in some other conditions, I made an extended investigation into their nature.[11] It can be shown that they contain cholesterin and, in some cases, fatty acids. I therefore experimented with pure cholesterin and other chemical substances in order to find out under what conditions the peculiar doubly refracting globules could be obtained. I found that if choles-

terin was melted with one of the higher fatty acids or certain alcohols and other substances, the globules appeared during the cooling of the preparation, and that the mixture subsequently solidified in the form of crystals closely resembling the crystals found in the sections.

It is fairly certain that these crystals in the tissues consist of cholesterin in loose combination with other substances. What the associated substance is cannot always be detected. Often it is a fatty acid as shown by the staining reaction of the globules resulting from melting the crystals; at other times they do not show the fatty acid reaction. It is probable that lecithin is one, perhaps the commonest of these associated substances, but we have no reliable means of detecting lecithin with the microscope. When these cholesterin mixtures are in the crystalline fluid condition they display certain peculiar physical properties. They can form an emulsion with water and it appears that cholesterin exists normally in the body as a colloidal solution or fine emulsion in association with lecithin or fatty acids, the cholesterin and the associated substance helping to keep each other mutually in solution in the body fluids. It is certain that cholesterin plays an important part in cell life, and the presence of these crystals in cancers, apart from any evident degeneration, suggests that cholesterin may be associated in some way or other with the regulation of cell proliferation.

As bearing on this point I may mention that spermatozoa are very rich in cholesterin, a fact which points to its being of importance to the developing embryo.

Another interesting point in this connection is the fact that gall stones are 2½ times as common in patients with carcinoma as in patients of similar ages suffering from other diseases.

The origin of Cholesterin is not certainly known but, from my observations, it would seem probable that it is secreted by the cortex of the adrenal body. I have examined a large number of adrenals and I find in every case crystals, resembling the crystals found in cancers, consisting of Cholesterin in association with other substances (Figs. 29, 30, 31). Usually these crystals occur in great masses filling the whole cortex and giving rise to the condition often called fatty degeneration of the

adrenal. It is, however in no sense a degeneration. It appears to be a normal condition and it seems as though the function of the adrenal cortex is to secrete Cholesterin and to pass it into the blood.[13]

Now we find that maldevelopment of the adrenals is usually associated with maldevelopment of other parts, especially of the brain, or with infantilism. On the other hand, hypertrophy and tumours of the adrenal cortex in children are associated with sexual precocity or with gigantism. Hence it would appear that the secretion of the adrenal cortex has some share in the mechanism of the control of growth and development. These observations, then, suggest that Cholesterin is elaborated in the adrenal cortex and that it plays some part in the regulation of cell proliferation.

I may mention that, some years ago, Mr. Holden Webb of Melbourne, suggested that Cancer was due to the crystallisation of Cholesterin from the living cells and he proposed a method of treating Cancer by hypodermic injections of soap solution, the idea being that the soap would help to keep the cholesterin in solution. Mr. Webb's suggestion appears to have been pure hypothesis as he did not detail any evidence on which it was founded.[9]

## Physiological Equilibrium.

We have next to determine why an extrinsic causal factor, which normally gives rise to inflammatory or compensatory changes, occasionally gives rise to tumour formation.

An epithelial cell is acted upon by the influences of the contiguous epithelial cells and also by the influence of the subjacent connective tissue. Normally these influences are in equilibrium with the intercellular proliferative forces. At the free surface, there being no antagonistic influences, the activity of the cell is manifested by proliferation, as in the skin and mucous membranes, or by secretion as in glands, or by absorption. Similarly a connective tissue cell is subject to the influences of the neighbouring cells which are in equilibrium with the proliferative forces within the cell.

Now the changes that occur when the equilibrium is disturbed will differ according as the original condition of equilibrium was *stable* or *unstable*. If the condition was stable any disturbance, by removing the influences, will be followed by proliferation of the cell which will continue until the influences of the neighbouring cells are again restored when the proliferation will cease. On the other hand, if the original condition of equilibrium was unstable, the intercellular influences will not be restored and proliferation will continue. Take, for example, an epithelial cell, the proliferative forces of which are in equilibrium with the restraining influences of the neighbouring cells. If we disturb the equilibrium by removing some of the neighbouring epithelial cells, the proliferative capacity is set free in the direction of the removed influence. The cell therefore commences to proliferate and, if the original condition of equilibrium was stable, proliferation will continue until, by the replacement of the cells which had been removed, the intercellular influences are again restored when proliferation will cease. This sequence of events we see in the regeneration of epithelium which follows an abrasion or a wound. If, however, the original condition of equilibrium was unstable, the intercellular influences will not be restored. Hence proliferation will continue indefinitely thus giving rise to a papilloma or an adenoma. If, instead of removing the influence of the neighbouring epithelial cells, we disturb the equilibrium by removing the influence of the subjacent connective tissue, then, if the original condition of equilibrium was stable, the cell proliferates for a time and then ceases as the restraining influences are restored. This is seen in the traumatic epithelial pearl produced by the displacement of epithelial cells into the subjacent connective tissue. If, on the other hand, the original condition of equilibrium was unstable, the restraining influences will not be restored and proliferation will continue in the connective tissue thus giving rise to a carcinoma.

Similarly in regard to the connective tissue cell, disturbance of the equilibrium, if stable, leads to regeneration and repair, but if unstable the result is a histioma if the relation between the cells and intercellular substance continue normal, or a

sarcoma if the cells proliferate without producing the intercellular substance.

Similar conditions occur with regard to functional activity. The functional equilibrium, just as the structural, may be stable or unstable and the result of disturbance is accordingly compensatory or progressive Hyperergasis.

We can say, then, that a tumour arises from a disturbance of a position of unstable equilibrium between the proliferative forces within the cell and the antagonistic influences of the neighbouring cells. The characteristic feature of an unstable condition of equilibrium is that it needs only a very slight force to upset it, hence the same extrinsic factor which, under normal conditions, only produces a temporary disturbance, will, if the equilibrium be unstable, give rise to tumour formation. An injury to a bone usually gives rise to a fracture with subsequent healing or to a periosteitis with subsequent recovery, but a similar injury may, in some cases, be the starting point of a sarcoma of other tumour.

The instability of equilibrium is probably a local condition as a rule but it is possible that it may occur as a general diathetic condition.

While the instability of equilibrium will explain the origination of a tumour it will not explain its extension to distant parts and its continued growth in metastatic nodules and in transplanted tumours. We have seen that cancer cells must be regarded as unicellular organisms which, while they may form new associations among themselves, have lost the power of forming secondary connections with normal tissues through which restraining influences could pass. Moreover it is possible that the cells, by their escape from the control of the organism, have acquired an increased capacity for proliferation—a habit of growth—which continues in the sites of metastatic nodules. The cancer cells therefore continue to proliferate as long as they are supplied with the necessary nutriment and the reaction of the surrounding tissues is of the same kind as the reaction caused by parasites or foreign bodies. The growth in metastatic nodules is usually more circumscribed and less infiltrative than

at the primary site where the condition of unstable equilibrium exists.

The immediate essential causal factor of tumour formation is thus an *unstable condition of equilibrium* between the component parts of the body, and the next question we have to consider is: What are the causes of this instability?

### The Influence of Inflammatory Conditions.

It has long been known that chronic inflammatory conditions may lead to Cancer. A chronic ulcer of the leg may continue for years without appreciable alteration, but the continued irritation may at length so alter the condition of the tissues that the equilibrium becomes unstable, when the result is tumour formation. Similarly Carcinoma may start in a chronic gastric ulcer, or in connection with the chronic inflammatory changes produced by Lupus or Bilharziosis, and Sarcoma may arise from the callus of a healing fracture. Also Leucoplakia of the tongue is said to be a frequent precursor of Carcinoma. The irritants in these cases do not act directly on the epithelial cells, but they so alter the connective tissue that the equilibrium between it and the epithelium becomes unstable so that tumour formation follows. In Bilharzial Carcinoma, as Dr. Harris pointed out, the ova, which are the irritating factors, are not situated in the growth itself but in the neighbouring connective tissue.[5] (Figs. 32, 33.)

Other examples of chronic irritation producing cancers are seen in the influence of clay pipes, jagged teeth, etc., on the occurrence of cancer of the mouth.

During the proliferative changes which accompany these inflammatory conditions it is very likely that certain tissue cells will become separated from their normal connections. Such isolated cells may form the rudiments from which a tumour may arise, either during the progress of the inflammation, or, after it has healed, from the scar.

### The Influence of Heredity.

It is impossible to obtain reliable statistics as to the part played by heredity in cancer because it is only in rare instances

that we can obtain a reliable family history. There is no doubt, however, that cancer does occasionally run in families and this is what we should expect.

In many cases, however, the tendency to cancer in an individual is not so much due to heredity as to a want of heredity—it may arise in the individual as a spontaneous variation or mutation. It is these spontaneously arising cases that we should expect to be handed on to the descendants by heredity since it is an accepted fact that variations tend to be inherited. On the other hand, cases of acquired cancer, such as those arising in connection with chronic irritation, we should not expect to be transmitted to descendants as it seems clear that acquired characters are not inherited.

### The Influence of Civilisation.

There can be little doubt that the various influences grouped together under the title of civilisation play a part in producing a tendency to Cancer. It is difficult to obtain statistics with regard to Cancer in uncivilised races and wild animals but it seems certain that, while Cancer is not unknown under these conditions, it is much more rare than among civilised races and domesticated animals. It is probable that no one factor in civilisation is responsible but that it is the condition as a whole that is at fault. Unnatural and excessive food, unhealthy surroundings, indoor and sedentary occupations, and the mental anxiety and worry which are inseparable from civilised life probably all take a share in producing a wear and tear of life that is conducive to the formation of an unstable condition of equilibrium.

### The Influence of Sex, Age, and Site.

When we come to study questions regarding the incidence of Cancer, we are met with the difficulty of obtaining reliable statistics from which we can deduce conclusions. To be of any value the statistics must deal with a sufficient number of cases to eliminate accidental fallacies and each case must be verified microscopically by a competent histologist. Even if this pre-

caution be taken a further difficulty arises in the fact that pathologists do not always agree as to the position of certain tumours. Endothelial tumours will by some be placed among the sarcomata and by others among the carcinomata, while others will allot them a class by themselves. Also some will include gliomata and myxomata with the sarcomata. The majority of the tumours which I have called Blastocytomata are included by others among the sarcomata although the fact that epithelium develops in them distinguishes them from the true sarcomata. Many place the mixed tumours of the parotid among the endotheliomata, without any good reason as far as I can see.

The returns of the Registrar General are not available for deducing conclusions regarding the incidence of Cancer owing to the want of accurate distinction between the different forms, and we are therefore practically confined to the use of hospital statistics which deal with cases selected as suitable for hospital treatment and are, therefore, of no value in determining the incidence of Cancer in the general population.

Bearing these difficulties in mind I propose to give a few results which can be obtained regarding the incidence of Cancer in respect to age, site, and sex, making use of the statistics compiled by the Imperial Cancer Research Fund from the General Hospitals of London (2 No. 2). Besides the error attached to hospital statistics mentioned above it must be remembered that these statistics are obtained from general hospitals and do not include cases from special hospitals such as hospitals for women and children. Hence the proportion of males to females does not represent the actual sex incidence and the statistics show an abnormally large number of cases of Carcinoma of the breast (1026) as compared with Carcinoma of the uterus (298). The statistics are, however, extremely valuable in that every case was verified microscopically by competent pathologists and hence valuable results can be obtained from a comparison of the figures *inter se*.

The statistics for Carcinoma deal with 1928 males and 2197 females and those for Sarcoma with 516 males and 391 females.

In comparing the carcinoma incidence in males and females we must remember that in females there are three situations

which have no counterpart in males. The breast, uterus, and ovaries are, throughout a considerable period of life subject to periodical variations in the activity of cell proliferation and in

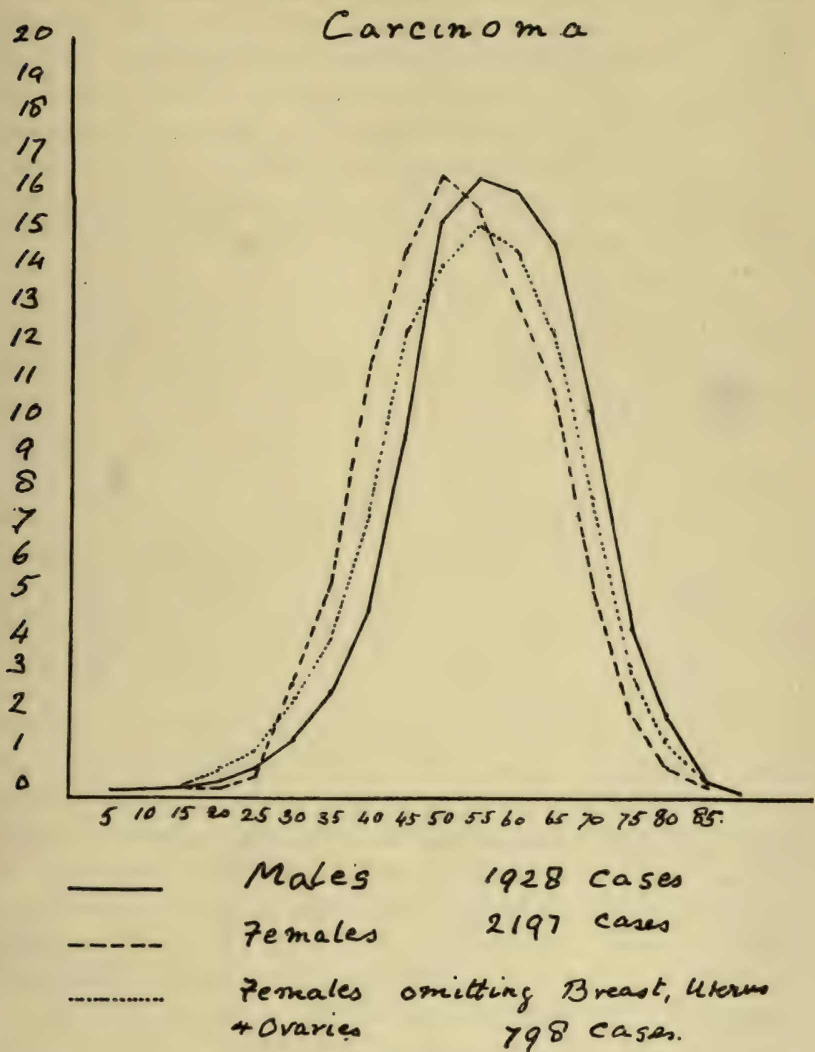


CHART 1.

the state of their blood supply. It is on this fact that the great liability of these organs to Carcinoma and other tumours depends. The breast, uterus, and ovaries together account for 1399 of the 2197 female cases of Carcinoma.

In the following charts which are compiled from these statistics the abscissæ represent the ages in quinquennial periods while the ordinates represent the number of cases per cent of the particular group of cases under consideration. For instance, the ordinates of the curve representing the incidence of Carcinoma in the male are calculated in percentages of the total male cases of Carcinoma and similarly for the other curves.

If we make a chart showing the age distribution of Carcinoma we obtain curves like those in Chart 1. One of these curves shows the distribution of the male cases, another of the female, and the third of the female cases omitting the breast, uterus, and ovaries.

All the curves are remarkably uniform and evidently follow a definite law. This will be found to be the case with all carcinoma curves which deal with a sufficient number of cases to eliminate fallacies.

We notice that all the curves commence to rise at about the age of 25, and, rising slowly at first and then rapidly, reach the maximum at 50 in females and 55 in males, subsequently falling rapidly. The effect of omitting the breast, uterus, and ovaries is to bring the female curve nearer to the position occupied by the male curve so that the maximum incidence occurs at the same age (55). The female curve is, however, still slightly in advance of the male curve.

We can conclude from these curves that age has an important influence on the incidence of Carcinoma.

If we plot out a similar curve for Sarcoma we find a marked difference (Chart 2). The curve starts at a moderately high point due largely to the inclusion of many blastocytomata. It descends rapidly to a minimum in the second and third age periods and then rises during the adolescent period. It subsequently remains at a high level with irregular fluctuations until it finally descends in old age.

It appears from these curves that age has not such a marked influence on the incidence of Sarcoma as it has in the case of Carcinoma. Omitting the initial high level due to congenital tumours, we see that the sarcoma curve rises rapidly during the adolescent period, while the carcinoma curve does not begin to rise markedly until after adult age has been reached.

If we study the age distribution of Sarcoma in different organs or groups of organs we notice several differences in the incidence. The curves, however, are not very reliable owing to the small number of cases in many situations. We find that if

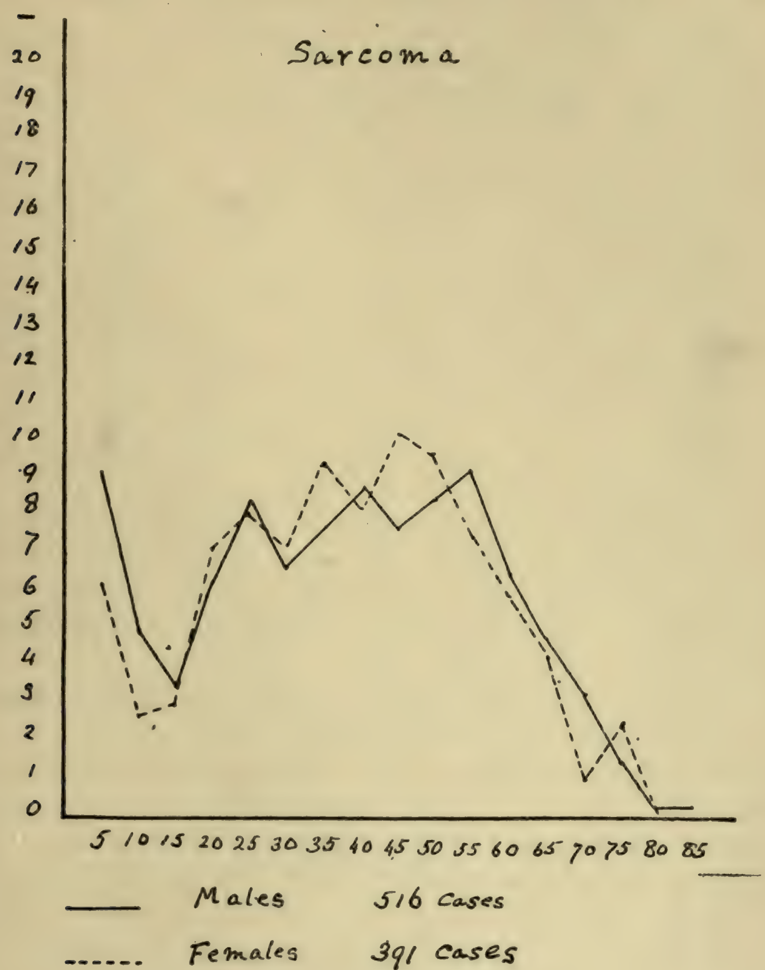


CHART 2.

we group together the glands—kidney, liver, pancreas, adrenal, and parotid—32 per cent. of the cases occur in the first age period owing chiefly to the inclusion of the blastocytomata.

If, on the other hand, we take the breast, uterus, and ovaries

we obtain a curve very similar to the carcinoma curve of the same organs but less regular.

Again, if we take the sarcomata of bone, we find that the curve rises rapidly during the adolescent period to a maximum

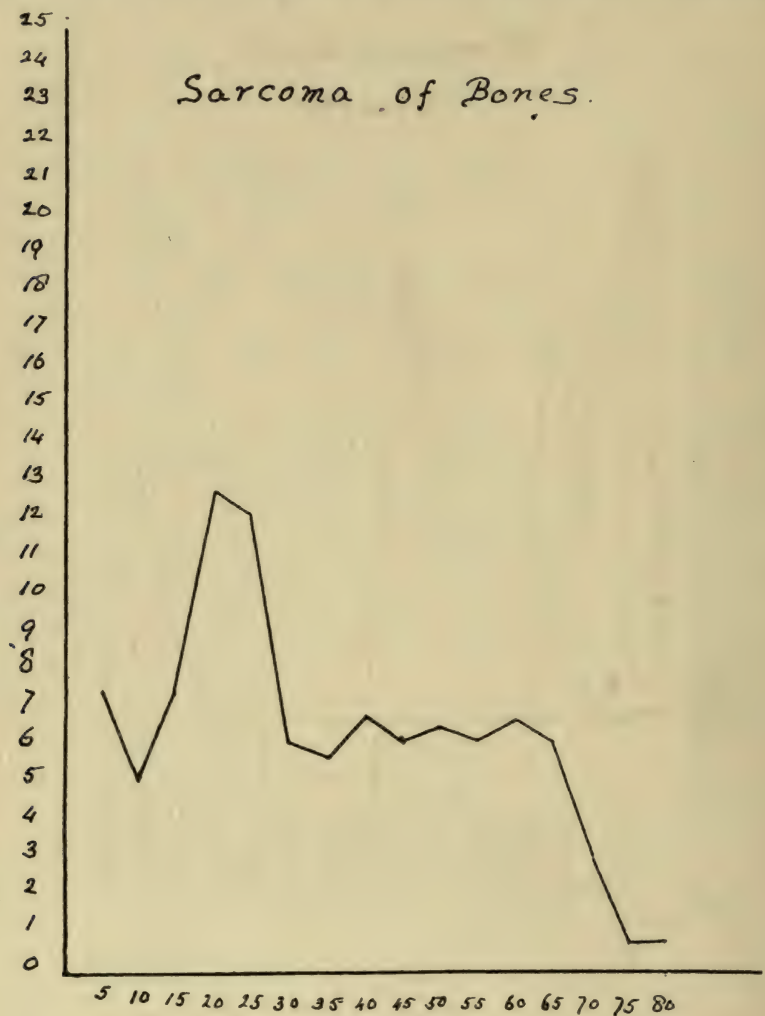


CHART 3.

at the age of 20—25, and then falls immediately to a level which is maintained almost constant until it falls at the age of 65. (Chart 3.)

Thus the age distribution in Sarcoma seems to follow no regular law. The one constant feature seems to be that the second and third age periods show the minimum incidence and that the incidence rises with adolescence.

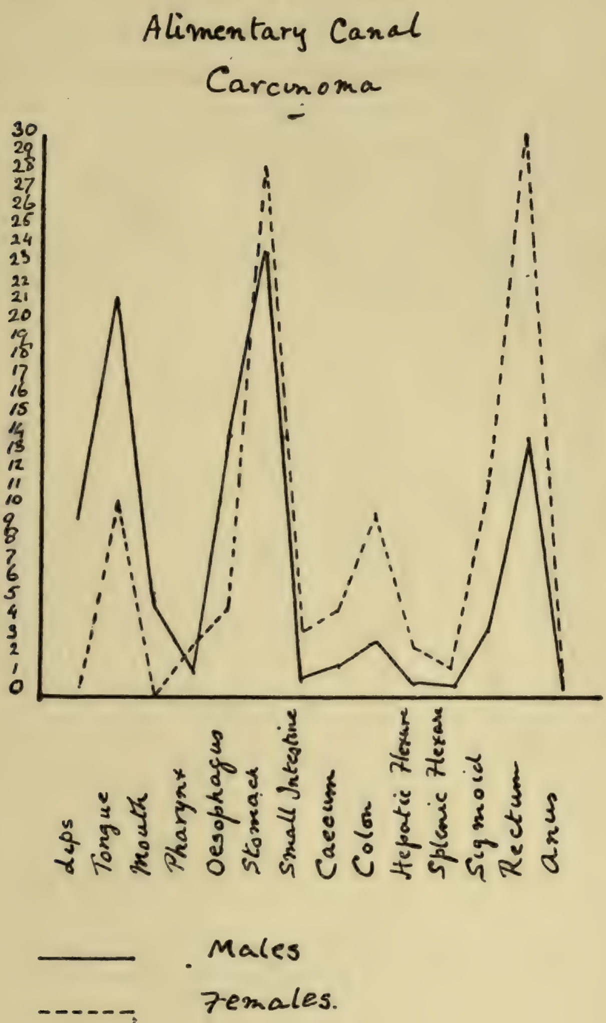


CHART 4.

On the other hand, the curves of the age distribution of Carcinoma in different situations all show a remarkable resemblance to one another, rising rapidly, after adult age has been

reached, to a maximum and then falling equally rapidly, the actual position of the maximum varying slightly in different cases.

If we compare the distribution of Carcinoma in the alimentary canal in males and females, we find that, as we should expect, the distribution is very similar in the two sexes, both curves showing identical variations. (Chart 4.) About the same proportion of cases in both sexes occurs in the stomach, but we notice that the male curve is higher in the parts above the stomach, while the female curve is the higher in the lower parts. While over 50 per cent. of the male cases occur above the stomach, over 50 per cent. of the female cases occur below.

This difference is presumably due to differences in the habits of the two sexes.

## Part IV.

# THE BEARINGS OF PATHOLOGY ON TREATMENT

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### Recapitulation.

I propose now to consider the principles on which the treatment of Cancer should be based. First it will be necessary to recapitulate the facts which we know about the disease.

(1) Proliferation is an inherent property of the cell. Normally this power of proliferation is kept in check by the influences of the organism as a whole exerted through adjacent cells.

(2) The essential causal factor in tumour formation is an intrinsic one, namely the continued removal or diminution of the influences which restrain proliferation.

(3) This intrinsic factor may be of intrinsic origin alone or may arise from the action of extrinsic causal agents, as, for example, in chronic irritation.

(4) The extrinsic causal factors are not of a specific kind but are the agents we know generally as irritants.

(5) The extrinsic causal factors act partly by so influencing the tissues as to give rise to the intrinsic conditions which I have called *instability of equilibrium.* They also act as determining factors in determining the appearance of a tumour when the necessary intrinsic conditions are present.

(6) In either case the tumour itself at its first appearance is a purely local condition.

(7) Certain chronic inflammatory conditions are sometimes followed by cancer. Unfortunately we cannot say in any given case whether a given inflammatory condition will be followed by Cancer or not. We cannot diagnose with certainty a precancerous condition.

(8) Age has a marked influence in determining the incidence of Carcinoma but its influence in the case of Sarcoma is less marked.

(9) Tumours arise from normal tissues, from aberrant rudiments, or from pre-existing tumours.

(10) Tumours grow by proliferation of their own cells but the area of origin may show some extension. To this extent only do the surrounding tissues contribute to the growth of the tumour.

(11) Cancers extend mainly by infiltration of the surrounding parts, the proliferating cells penetrating the tissue spaces.

(12) The next stage of the process of extension is the permeation of lymphatics, veins, and other natural channels. In this process the cells grow continuously along the channels and the direction of the extension is not determined by the direction of the lymph or blood stream. During permeation of lymphatics in external cancers the extension is greater in the deep fascia than in the superjacent skin or subjacent muscle.

(13) By this process of permeation arise cutaneous nodules, invasion of bones, infection of the regional lymph glands, and, perhaps, invasion of the serous cavities.

(14) In the last stage of extension the cancer cells are detached and carried along by the lymph or blood stream or along mucous canals and give rise to metastatic deposits, *i.e.*, to deposits at a distance from the primary growth.

(15) Cancers, in some animals, can be transplanted to animals of the same species and cells displaced from a tumour can continue to proliferate.

(16) Tumours sometimes disappear spontaneously.

(17) In experimental cancer it is found that when a tumour has disappeared the animal subsequently shows some immunity. This immunity is specific, being most marked for the identical tumour from which the animal has recovered, less marked for other tumours of the same genus, and absent for tumours of another genus.

(18) Since the cells of which the tumours are composed are identical with normal cells it is probable that the metabolism in them is identical with the metabolism of the cells of origin.

making allowance for the rapidity of proliferation in tumour cells.

(19) Cancers and other tumours are liable to the occurrence of the same pathological processes as normal tissues. They can show inflammation, degenerations, necrosis, etc.

(20) Tumours in their growth give rise to an inflammatory reaction of the surrounding parts, resembling the reaction against foreign bodies, etc.

(21) While a simple tumour is to be regarded as an individual—a multicellular organism—a cancer is rather a colony of unicellular individuals.

(22) Cancer is truly described as an infection by cancer cells.

## Principles of Treatment.

In estimating the value of any mode of treatment in the case of Cancer two points must be borne in mind. The treatment must be tried in a sufficiently large number of cases to eliminate fallacies due to coincidence, etc., and all cases must be verified histologically by a competent pathologist.

We must also remember that cancers are often surrounded by an inflammatory zone which causes the dimensions of the tumour to appear greater than the actual size. Hence an apparent improvement after treatment of any kind, as shown by a diminution in size, may be entirely due to a diminution in the inflammatory zone with absorption of the products of inflammation while the actual tumour may not have been influenced at all.

It is much to be regretted that the writers and compilers of text books of medicine seem to habitually ignore the subject of Cancer. Cancer, however, has its medical aspects as well as its surgical, and we require more clinical observations on Cancer from the medical point of view.

Since a tumour is a self-contained structure having in itself the power of growth, the most obvious method of treatment is to remove it entirely from the body. In this, the surgical treatment of Cancer, there are several points to be noticed. In the first place cancer cells are themselves infective and if the wound be contaminated with them recurrence is likely to occur. In

removing a cancer, then, care must be taken that the growth is not cut into during the operation. In the next place the growth infiltrates the surrounding tissues to a distance beyond that which can be estimated by microscopic examination. Hence the tumour must be removed with a sufficient margin of healthy tissue. Again Cancer spreads by permeation along lymphatic trunks and the extent of this permeation, in the case of external cancers, is greater in the deep fascia than in the superjacent or subjacent tissues. Hence the deep fascia should be removed to a greater extent than the skin. Mr. Handley, who has made a study of permeation in external cancers recommends that the deep fascia should be removed to an extent of two inches beyond the skin incision.[4] This permeation may extend to the regional lymph glands so that these should always be removed in continuity with the deep fascia and the primary tumour. The permeation also extends to an approximately equal extent in all directions from the primary growth and is not confined to the direction of the lymph current, so that the tissues should be removed to an equal distance all round the original tumour.

When metastasis has occurred the case may be regarded as beyond the limits of surgical operation.

Provided that the operation has included the removal of the whole tumour with its ramifications into the surrounding tissues this mode of treatment offers a prospect of complete cure.

Apart from removal, several attempts have been made to destroy the cancer cells *in situ* by caustics, etc. Unfortunately we do not know of any substance which has an injurious effect on the cancer cells which does not at the same time have a similar effect on the surrounding tissues. Among the caustics may be mentioned Potassium bichromate, and Potassium permanganate, both of which have been recommended. Another agent which has been recommended as having a special effect on cancer cells is Trypsin. This agent, about which we have heard so much, is supposed to act partly by its digestive properties and partly by the action of the associated amylopsin on glycogen.

Apart from attempting to destroy the cancer cells *in situ* we might attempt to starve them by cutting off their blood supply.

It is, however, impossible to do this without at the same time starving the surrounding tissues, because the blood supply of a cancer is derived on all sides from the neighbouring parts. This method, then, is only applicable as a palliative method in rare cases.

If we could detect a substance which was necessary for the metabolism of cancer cells to a greater extent than for the normal tissues we might approach the treatment through this substance. Some people have thought that glycogen is such a substance, but recent researches have shown that glycogen is not present in all tumours and that its presence does not depend on the malignancy so much as on the tissues from which the tumour springs. It is obvious that if glycogen had been essential for the proliferation of the cancer cells we might have attempted the treatment by taking steps for the elimination of the excess of the glycogen.

It is possible that some substance will yet be found through which to approach the subject of treatment.

Mr. Holden Webb, on the basis of his hypothesis that Cancer is due to the crystallisation of cholesterin out of the living cells, suggested the use of hypodermic injections of soap solution with the idea of supplying a solvent for the cholesterin.[9]

Another possible manner of approaching the treatment of Cancer would be to induce the tumour so to alter its mode of growth as to behave as a simple tumour. The tumour would then limit itself and so would be more amenable to surgical treatment. This idea is purely hypothetical as we have no knowledge of the influences which determine malignancy or non-malignancy.

Apart from any mode of treatment directed to the tumour itself we can conceive of modes of treatment directed towards increasing the resisting powers of the surrounding tissues. If we could restore the influences normally existing between the component parts of the tissues involved, we should succeed in causing the proliferation to cease and retrogression to set in. Here again we are met with the difficulty that we are at present totally ignorant of the nature of these influences, but some slight progress has been made chiefly in connection with X rays

and Radium, both of which appear to act by setting up an inflammatory reaction in the surrounding tissues combined with some destructive action on the tumour cells themselves. This method is most applicable in the case of cutaneous cancers, and the X ray treatment of Rodent ulcer and superficial squamous-celled carcinomata is admitted to be of considerable value.

Here also may be included suggested remedies such as Sodium cinnamate, and cumarate, which produce a general leucocytosis, also Coley's fluid which probably acts in a similar way.

Tonic treatment, especially arsenic, may be expected to raise the general resistance of the body tissues, and cases of amelioration under arsenic have been described. It is interesting to notice in this connection that arsenic has also a considerable beneficial effect on other diseases which are of a progressive nature, such as Hodgkin's disease, Leucocythæmia, Graves' disease, Diabetes insipidus, etc.

Another method which suggests itself is the general hygienic treatment including fresh air, exercise, freedom from worry, suitable diet, etc., which plays such an important part in improving the well-being of the body generally. We know that this method of treatment is proving of great value in infection by the tubercle bacillus and it is, perhaps, worth while to consider whether it would not have a similar effect in infection by cancer cells.

Another possibility in methods of treatment is in the use of extracts of glands which have an internal secretion. It is known that the pituitary, thyroid, and adrenals, have some effect on growth but what that effect is is not yet known. Thyroid treatment has been tried in some cases and at the Christie Hospital we have tried pituitary extract in two cases but without result. Thymus extract has also been tried. Removal of the ovaries and testicles has been tried in some cases of inoperable cancer with apparent benefit in some cases, but we must not forget that in the opinion of some authorities the removal of the ovaries increases the liability to Cancer.

Lastly we have empirical methods of treatment which may be described as modes of treatment tried hap-hazard without

any scientific basis. Such methods are violet leaves, molasses, chian turpentine, etc. We may say that no substance has yet been found that has any effect on Cancer, nor is it likely that any substance will ever be found which has any effect comparable with that of quinine in Malaria since Malaria is due to an extrinsic agent while Cancer is, as we have seen, an infection by cells derived from the body cells, and it is hardly possible to conceive a substance which will destroy the tumour cells without at the same time destroying their near relations, the body cells.

With regard to the effects of these different modes of treatment we can say that, apart from surgical operation, and, in special cases, X-rays or radium, none of the numerous suggested remedies have proved of any permanent value. Cases of amelioration during treatment of various kinds have been described, but further investigation has always shown that these cases of improvement are accidental and cannot be ascribed to the immediate effect of the treatment. Some of these cases of improvement are due to the lessening of the pericancerous inflammation producing an apparent diminution in the size of the tumour.

When the case is operated upon early enough to allow of complete removal we have a fair prospect of complete cure. When, however, it has gone beyond the limits of surgical operation the prospects are at present almost hopeless. Surgery and medicine can still do much in the way of palliative measures but we know of no remedy which will effect a cure.

I may say that all suggested methods of treatment, whatever their origin, are given a fair trial at the Christie Hospital provided that the use of them does not involve danger to the patient.

It appears most reasonable, in considering possible modes of treatment, to direct our attention more towards improving the general condition of the patient so that his tissues may resist the growth of the tumour, rather than to attempting to find a substance which will destroy the cancer cells without destroying the other tissues. It is possible, also, that if we can discover a chemical substance which is necessary for the proliferation of

the cancer cells, we may be able to approach the treatment of Cancer through this substance.

Whether or no we shall ever see a treatment by immunisation remains to be seen. I have mentioned that mice which have recovered from Cancer are immune to that particular cancer and, to a less degree, to other related forms, and, if this mode of treatment ever becomes possible, it would seem probable that it will consist in immunising a patient against his own cancer.

With regard to preventive treatment the only means that can be suggested are ordinary hygienic principles and the prompt treatment of any chronic inflammatory foci that may occur.

## Conclusion.

I have now said what I have to say about Cancer. I have considered the pathology of the disease and have indicated the bearing of the facts of pathology on the indications for treatment. I conclude by reminding you that the problem of Cancer is the problem of Growth. When biologists can tell us what are the influences which determine the form and size of the living organism and of its constituent parts, then pathologists will be in a position to determine more exactly the nature of tumours. In the meantime all features in tumours must be investigated and such investigation must not be limited to tumours alone. Other diseases and normal processes must be included in the scope of the investigation, as also problems of chemistry and physics, before we can arrive at a complete answer to the question "What is Cancer?"

# APPENDIX

# APPENDIX.

## THE PARASITIC THEORY.

I have not thought it necessary in the lectures to enter into a full discussion of this theory as I went into the matter fully in my Erasmus Wilson Lectures in 1902.[10] The criticisms I then brought forward have never been answered, and it is a curious fact that the upholders of this theory never think it necessary to answer the criticisms brought against it, while they continue to bring forward again and again the same arguments in its favour. Very few of the leading pathologists have expressed an opinion in favour of the theory that the essential casual agent of Cancer is a parasite. The upholders of the theory are mostly surgeons or bacteriologists who do not appreciate the pathological and biological difficulties which the theory involves.

For the sake of those who are not well acquainted with the discussion which has ranged about this theory I here introduce a brief résumé of the argument.

The grounds on which the theory is based are:—

(1) *The apparent resemblance of Cancer to such infective diseases as Tuberculosis, etc.* I have considered this point in the lectures and I have pointed out that the only argument to be obtained from this resemblance is the argument that the cancer cells themselves are parasites.

(2) *The inoculability of Cancer.* If Cancer were due to a parasite we should expect infection of one person by another to be of frequent occurrence. Such cases are, however, extremely rare, and hardly more than could be explained by coincidence. The venereal growths which are met with in dogs are highly contagious, but it is not certain whether they are to be considered as true tumours or whether they are more allied to granulomata. Microscopically they show a close resemblance to sarcomata but they do not show the same power of infiltrating the surrounding tissues. Even if they be considered as sarcomata the fact that they are contagious is no argument in favour of their being of

parasitic origin, since the infecting agents may be the tumour cells themselves.

In the transmission of Cancer from mouse to mouse the new tumour arising is a direct continuation of the growth of the introduced portion and is not due to infection of the tissues of the new host.

(3) *The lesions produced in the rabbit's liver by the coccidium oviforme.* In coccidiosis we find local dilatations of the bile ducts filled with coccidia and epithelial debris. The younger forms of the parasite are contained within the epithelial cells while the older lie free in the cavity. In no case do we find any lesions at all resembling Cancer. The process appears to be of the nature of a catarrhal inflammation, the infected epithelial cells being cast off and the remaining cells proliferating to take their place. The coccidia are sometimes found in the connective tissue where they give rise to an ordinary chronic inflammation of the fibrous tissue.

(4) *The topographical distribution of Cancer.* Cancer has been supposed to occur endemically in certain localities or certain houses. The evidence, however, is not strong on this point nor are there any resemblances between the circumstances of different cancer districts. Some cancer districts are in valleys, others on hills; some are in moist situations, others in dry deserts, etc. It has been proved that the cells of a mouse cancer can retain their vitality for a long time outside the body under various circumstances and yet be able to proliferate on being introduced into a new mouse. Hence the endemic occurrence of Cancer is in itself no argument for the necessity of a parasitic causal agent.

(5) *The presence of certain cell inclusions, supposed to be of a parasitic nature and the possibility of obtaining cultures of bacteria, etc., from cancers.* It does not appear that any of the numerous observers in this field agree with others as to what the cancer parasite is. Bacilli, cocci, protozoa, blastomycetes, and moulds have all had their day. Each new observer points out the mistakes made by his predecessors and then brings forward a new parasite to be, in its turn, demolished by his successors. The inclusions described as parasites include various forms of

degenerative changes (hyaline, colloid, vacuolation, etc.), archoplasmic vesicles and centrosomes, extruded nucleoli, detached portions of nuclear chromatin, and, in all probability, globules of cholesterin. As regards cultivation experiments the same difficulties arise. There is no doubt that organisms can be cultivated from cancers in some cases, but there is no evidence that they have anything to do with the causation of Cancer. A large number of different bacteria and blastomycetes have been cultivated at different times, but no one has yet succeeded in reproducing undoubted Cancer on inoculating animals with the cultures of the suspected organisms.

Thus the grounds on which the theory is based are wholly inadequate. There are numerous other objections to the theory.

(6) *It is entirely unnecessary.* All the phenomena of Cancer can be explained on the supposition that the cancer cells are themselves the infecting agents. As I have pointed out, the capacity for proliferation is an inherent property of the cell as it is of all living organisms and it requires no parasitic theory to explain it.

(7) *The theory will not explain the origin of Cancer.* We know of no parasites which are capable of producing a primary proliferation of cells. The first effect of any irritant is destruction or injury to the cells. There is no evidence that in Cancer there is any initial injury. Even if we admit the existence of a parasite which produces a primary cell proliferation this would not explain Carcinoma, since the essential feature in Carcinoma is penetration of the epithelial cells into the connective tissue spaces.

(8) *The theory will not explain the growth of Cancer.* The reaction against any irritant, *e.g.*, Bacillus tuberculosis, is a centripetal proliferation of the tissue cells towards the irritant, whereas in Cancer the growth is centrifugal into the surrounding tissues.

(9) *It will not explain the site incidence of Cancer.* For example, it will not explain why the small intestine is so rarely the seat of primary Carcinoma, nor why the acini of the breast are more frequently affected than the ducts, nor will it explain why the breast and uterus are more frequently affected than other organs. In the case of Sarcoma we should have to

assume that the parasites are conveyed to the site of origin by the blood, and in that case we should expect to find that multiple primary growths were more common than they are.

(10) *It will not explain why there is an almost complete immunity to Carcinoma in the first twenty years of life.*

(11) *It will not explain the congenital tumours.*

(12) *It will not explain the occurrence of mixed tumours, such as the chondrosarcomata, etc., and especially the blastocytomata.*

(13) If all forms of Cancer are supposed to be due to the same parasite it is impossible to explain why metastatic growths always resemble the primary. We should expect, for instance, that a carcinoma would sometimes give rise to sarcomatous metastatic growths, and we should also expect that, if a carcinoma of the breast gave rise to a metastatic nodule in the liver, the latter would show the characteristics of a hepatic carcinoma, etc.

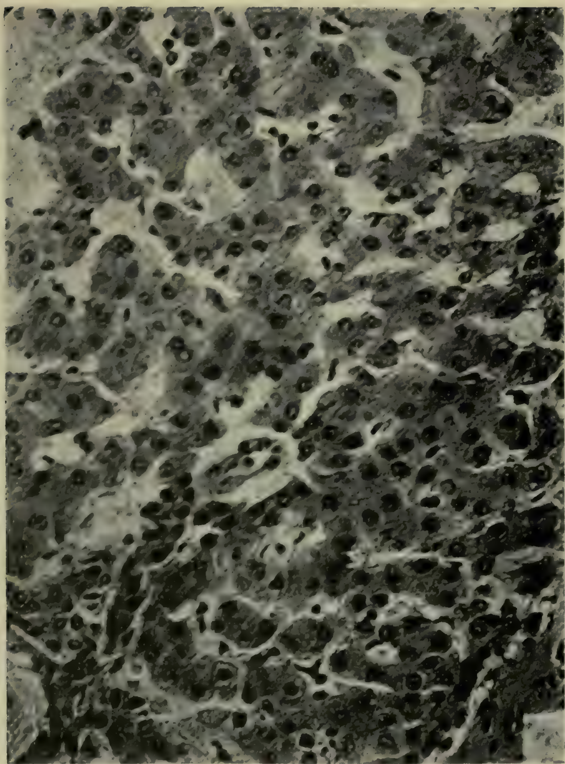
If, on the other hand, each kind of cancer has its own parasite we are met with the difficulty of the infinite variety of cancers. We should have to assume different parasites for all the different species of Carcinoma and Sarcoma, and we should have to imagine that each organ and tissue in the body has its own series of cancer parasites, and, moreover, that each species of animal has a different series of cancer parasites to every other animal.

(14) It is not usually contended that simple tumours are due to parasites, but, if they are due to extrinsic casual agents these agents must be of a parasitic nature since a continued and increasing growth demands a continued and increasing causal agent, if any agent is considered necessary. If it be contended that simple tumours are not due to extrinsic agents, then I answer that there is no justification whatever for separating the malignant tumours from the simple, and to say that while the simple are due to intrinsic factors alone, the malignant are due to the action of parasites.

We see then that the parasitic theory will not explain any of the phenomena, and that it vastly increases the difficulty of explanation.

We can say, then, that Cancer is not due to a specific parasite or parasites, but, on the other hand, we can say that the cancer cells themselves act as parasites. This latter view will explain all the phenomena of Cancer.

Fig. 1.



Tissue Tumour. Adenoma of the Liver.

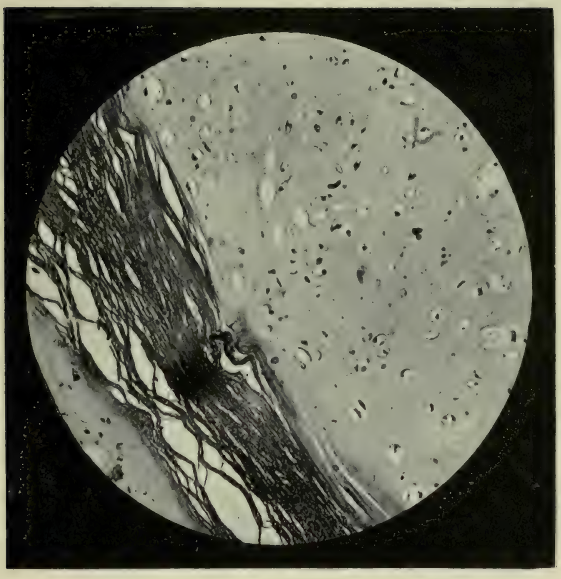
This is composed of cells, resembling hepatic cells, arranged in columns as in the normal liver. The tumour from which the section was taken was about 8 inches in diameter and was surrounded by a capsule. Throughout the whole tumour there was no arrangement of the cell columns into lobules and no ducts were found in any part of the growth.

Fig. 2.

Cell Tumour. Carcinoma of the Liver.

This is composed of cells, resembling hepatic cells, arranged atypically, showing no arrangement into columns as in the adenoma (Fig. 1).

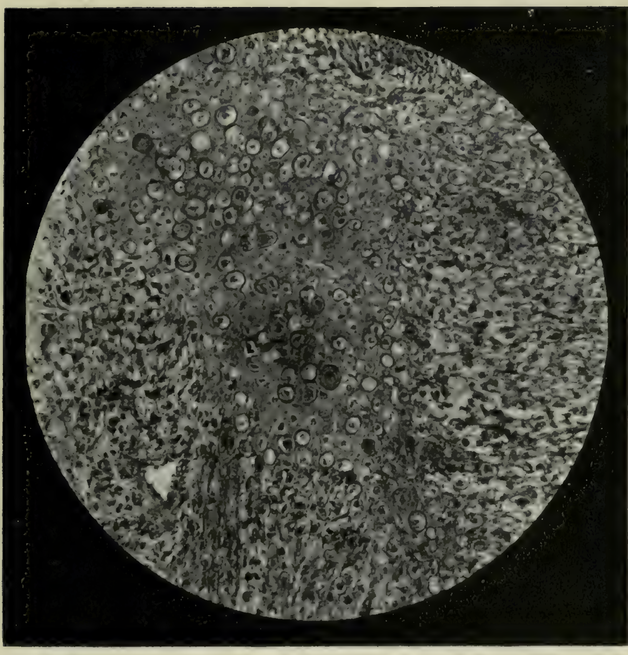
Fig. 3.



Tissue Tumour. Chondroma.

The nodules of cartilage, of which this tumour is composed, are everywhere surrounded by fibrous tissue.

Fig. 4.



Cell Tumour. Chondrosarcoma.

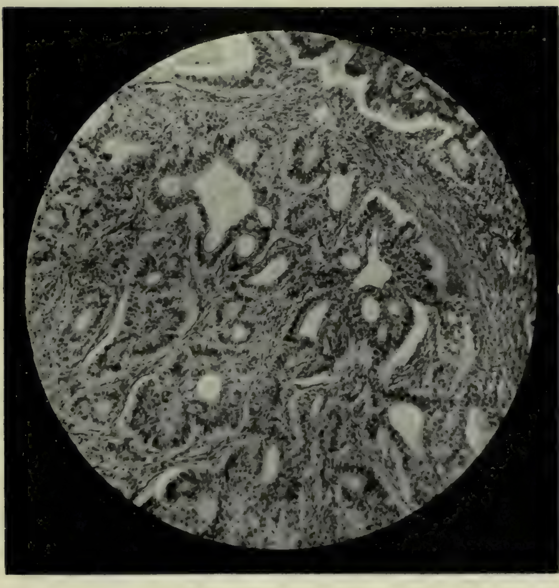
The nodules of cartilage are not sharply marked off from the surrounding sarcomatous tissue, but there is a gradual transition from one to the other, the sarcoma cells themselves becoming chondrocytes, thus giving rise to the cartilage as a secondary product.

Fig. 5.

Tissue Tumour. Adenoma of the Rectum.

The epicytes are everywhere arranged in definite tubes and sharply marked off from the surrounding stroma. There is no infiltration.

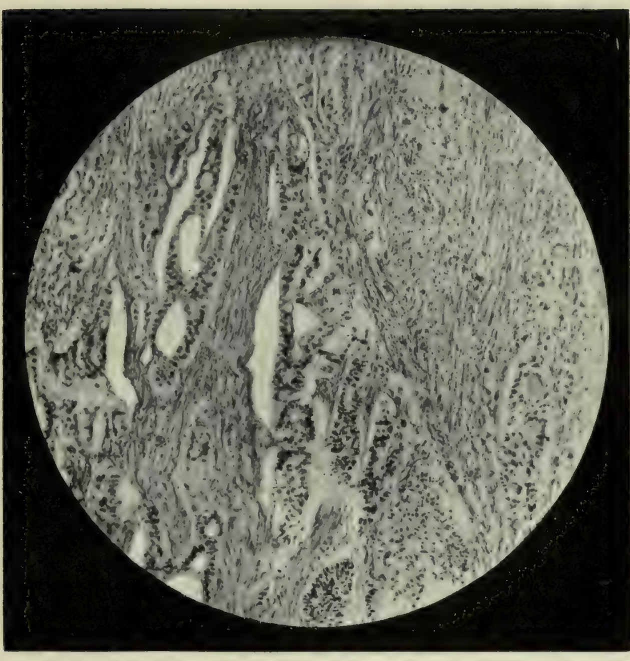
Fig. 6.



Cell Tumour. Carcinoma of the Rectum.

In this part of the tumour the structure somewhat resembles that of an adenoma. The tubes are, however, more irregular and in some places they are lined by several layers of cells.

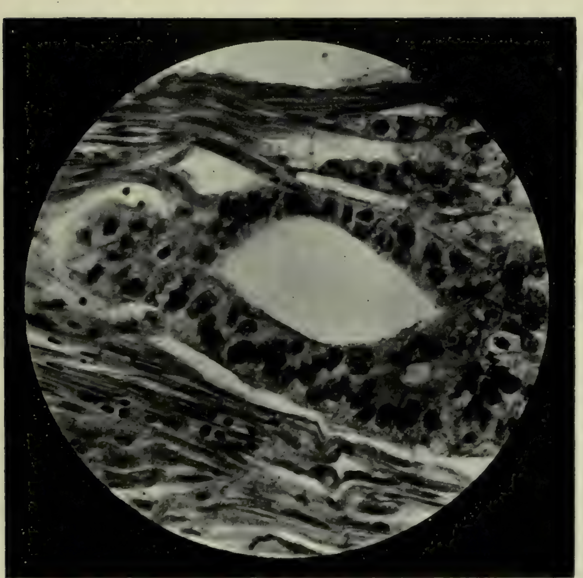
Fig. 7.



Cell Tumour. Carcinoma of the Rectum. From the same section as Fig. 6.

This shows solid columns of epicytes penetrating the surrounding connective tissue, the tubes being of secondary formation.

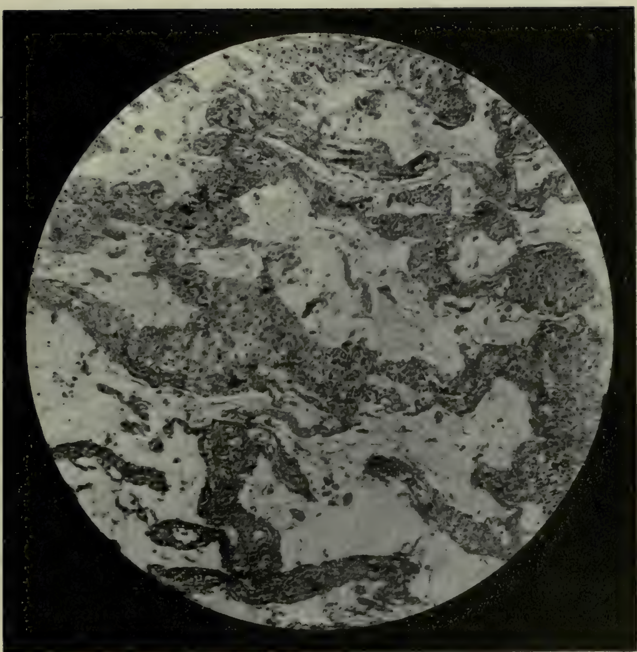
Fig. 8.



Cell Tumour. Carcinoma of Rectum. From the same section as Figs. 6 and 7.

This is a portion of Fig. 7 photographed with a higher power. It shows the formation of a lumen in a solid column of epicytes. Above are seen two other solid columns of cells penetrating the connective tissue.

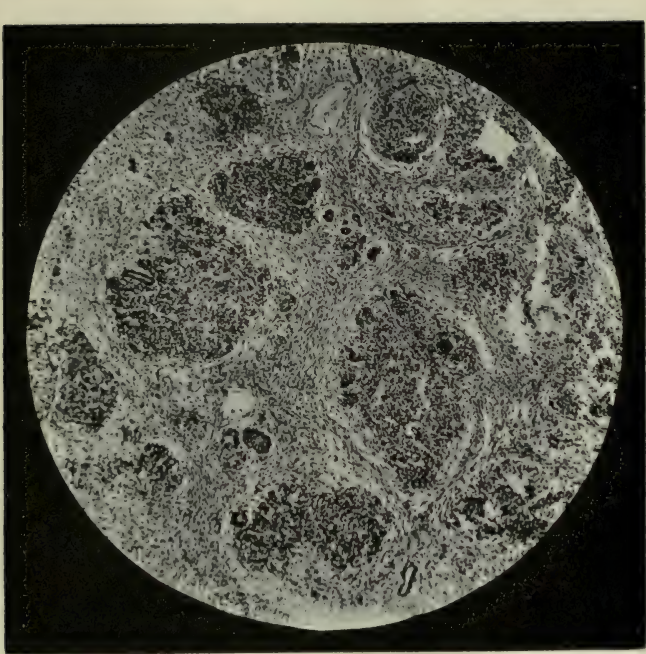
Fig. 9.



Angeioma of the Liver. (From Dr. Mantle's specimen.)

There are groups of hepatic cells in the septa between the cavernous spaces.

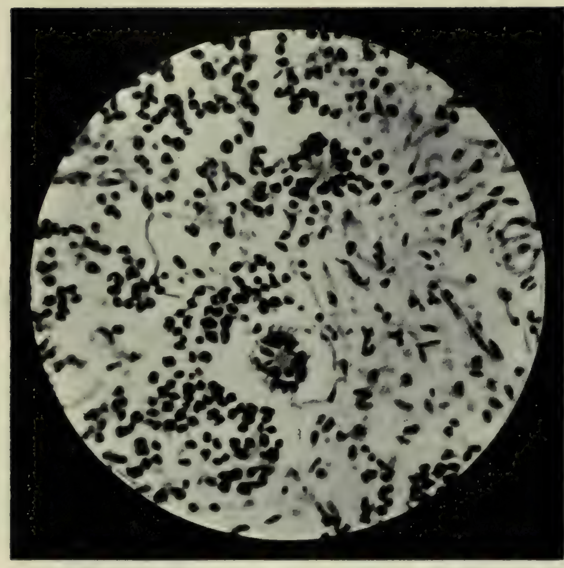
Fig. 10.



Blastocytoma of the Kidney. Low power.

The section shows groups of small round cells in which are embedded epithelial tubes. There are also strands of spindle cells running between the groups of round cells. Other parts of the tumour contained mucous tissue and smooth and striated myocytes.

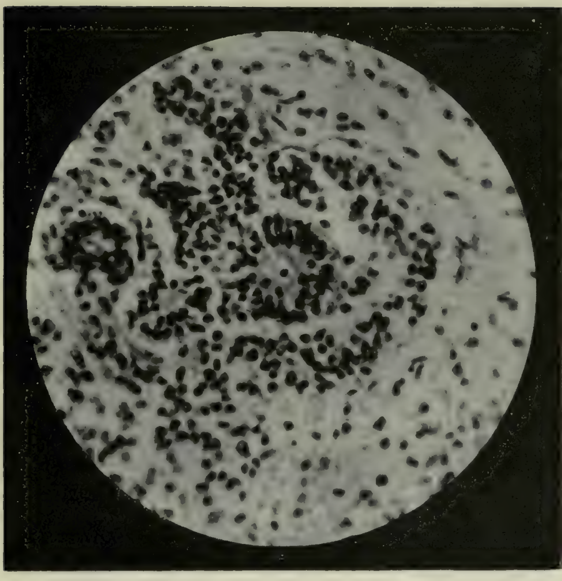
Fig. 11.



Blastocytoma of the Kidney. High power.

This shows the earliest stage of the formation of epithelial tubes from the round cells. In the upper part of the section is seen a group of the small round fundamental cells. Below this is another group slightly more advanced showing the commencement of the formation of a lumen.

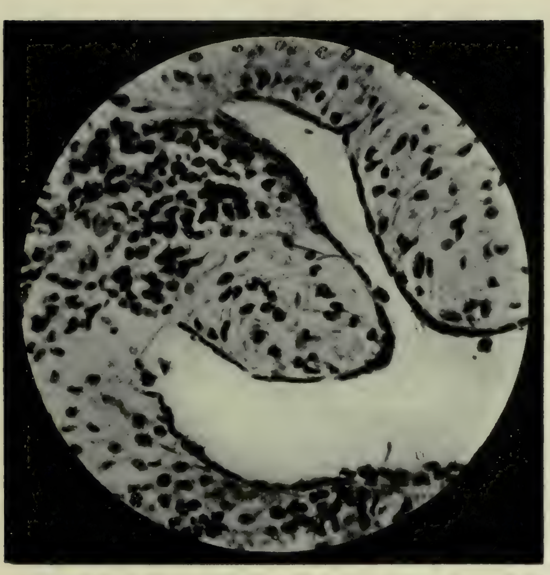
Fig. 12.



Blastocytoma of the Kidney. High power.

This shows a later stage in the formation of epithelial tubes. In the centre of the section is seen a group of cells with epithelial characters surrounding a lumen which contains débris and a detached cell.

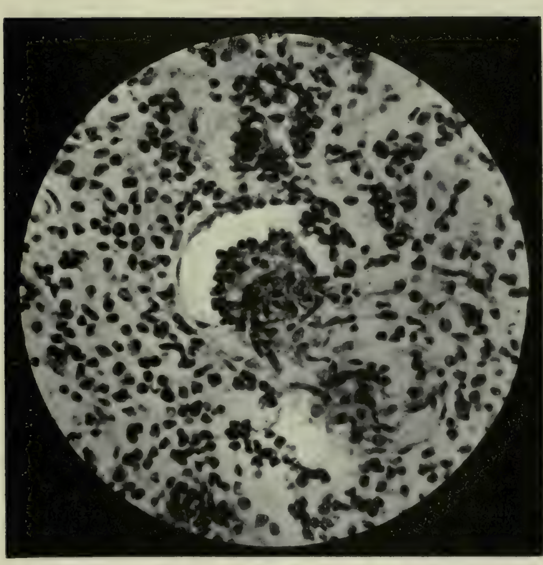
Fig. 13.



Blastocytoma of the Kidney. High power.

This shows a space lined with epicytes surrounded by mucous tissue. To the left is a group of the fundamental cells. There is no sharp demarkation between the epithelial cells, the mucous tissue cells, and the fundamental cells, all being connected together by cell-processes.

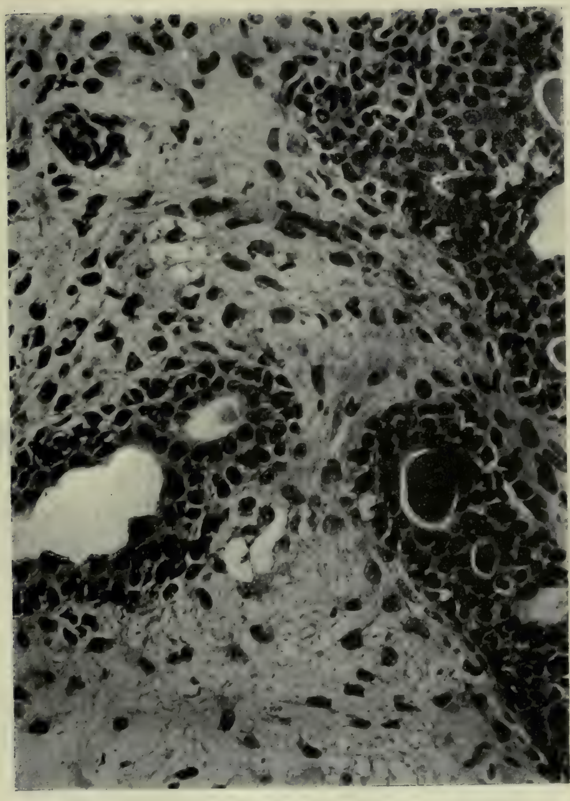
Fig. 14.



Blastocytoma of the Kidney. High power.

This section shows the invagination of one side of an epithelial tube to form a glomerulus-like structure.

Fig. 15.



Blastocytoma. Parotid Tumour.

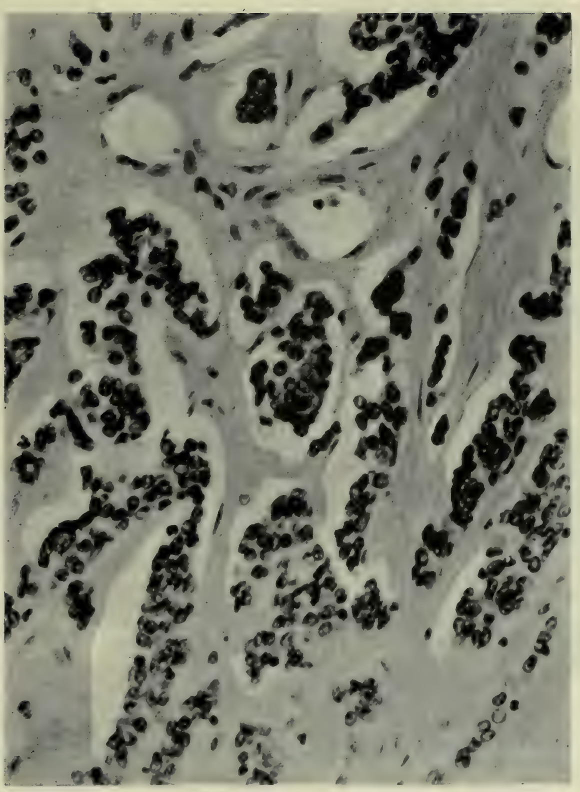
This section shows several groups of cells, embedded in which are epithelial tubes, some of which contain gelatinous material. The groups of cells are separated by areas of mucous tissue. There is no sharp demarkation between the different kinds of cells, the epithelial cells and the mucous tissue cells both passing gradually into the intermediate fundamental cells.

Fig. 16.

Primary Carcinoma of the Femur.

The cells in this tumour are of the epithelial type and, in places, are typically columnar in shape. There were no growths elsewhere in the body.

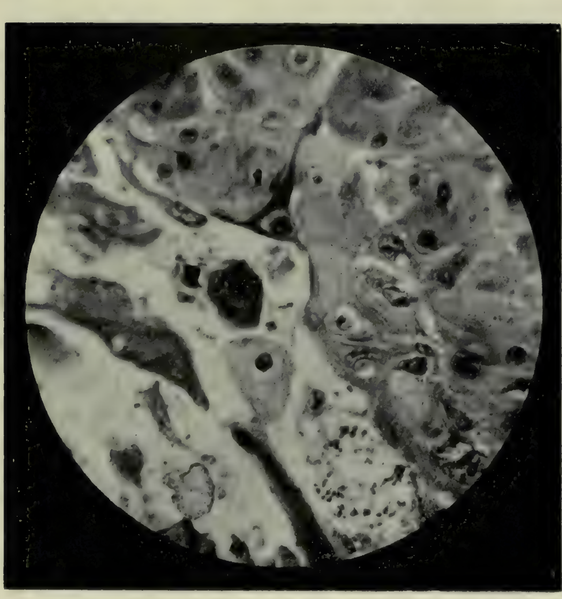
Fig. 17.



Primary Carcinoma of the Pleura. From a child aged 2.

This is a typical spheroidal-celled carcinoma.

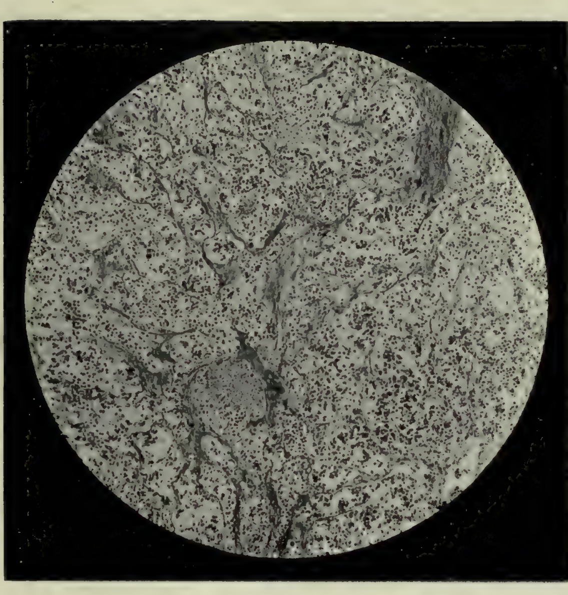
Fig. 18.



Primary Carcinoma of a Rib.

This shows typical squamous cells with prickles.

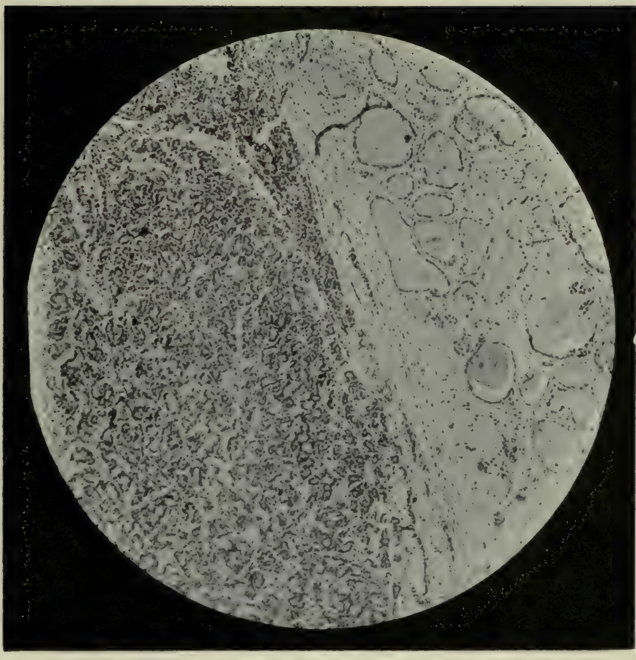
Fig. 19.



Sarcoma of the Neck. From a guinea pig.

This formed a tumour the size of a marble in the subcutaneous tissue of the neck. There was a similar growth in the neighbourhood of the pancreas.

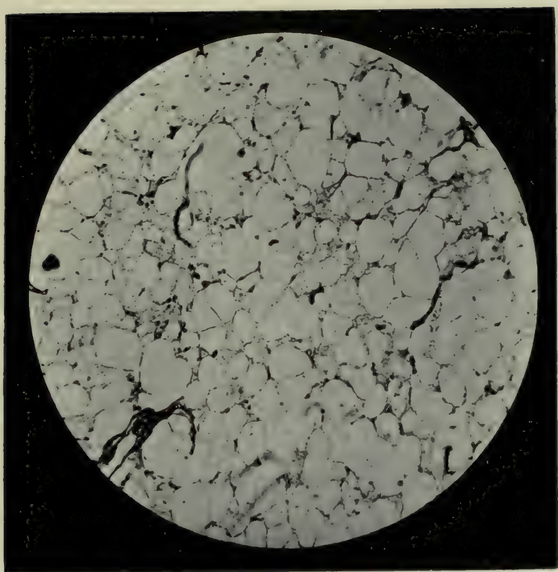
Fig. 20.



Carcinoma of the thyroid. From a mouse.

The dilated vesicles of the thyroid body are seen on the right of the photograph, the carcinoma being to the left. There were secondary tumours in both axillæ. Some of the tubes in the primary and secondary tumours contained some colloid secretion.

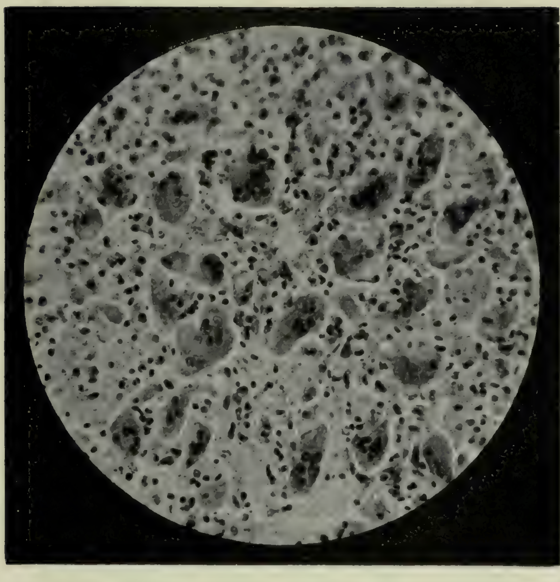
Fig. 21.



Lipoma. From a parrot.

This was a large tumour in the subcutaneous tissue covering the pectoral muscles. It shows the typical structure of a lipoma.

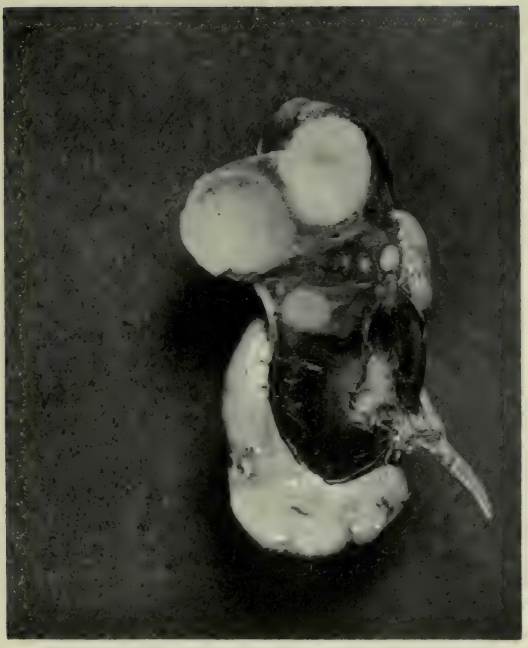
Fig. 22.



Giant-celled Sarcoma of the Femur. From a drake.

This is a typical giant-celled sarcoma. There were secondary growths in the liver.

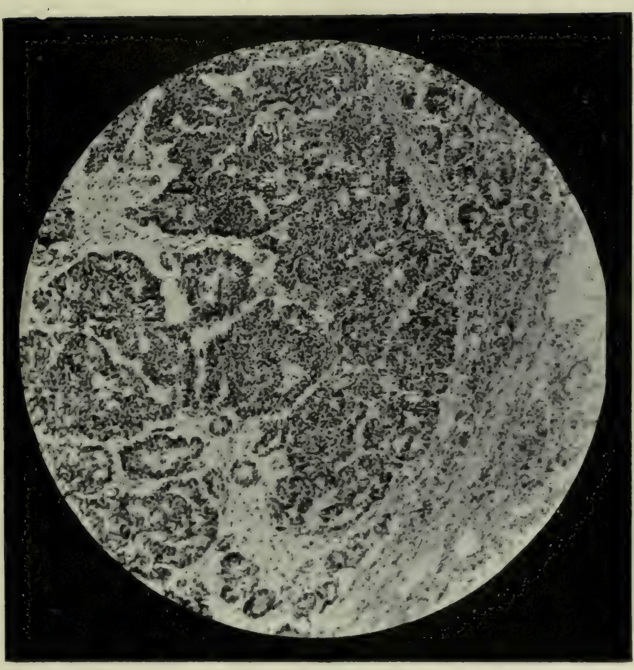
Fig. 23.



Carcinoma of the Kidney. From a rabbit.

There are several nodules of growth in the upper pole of the kidney.

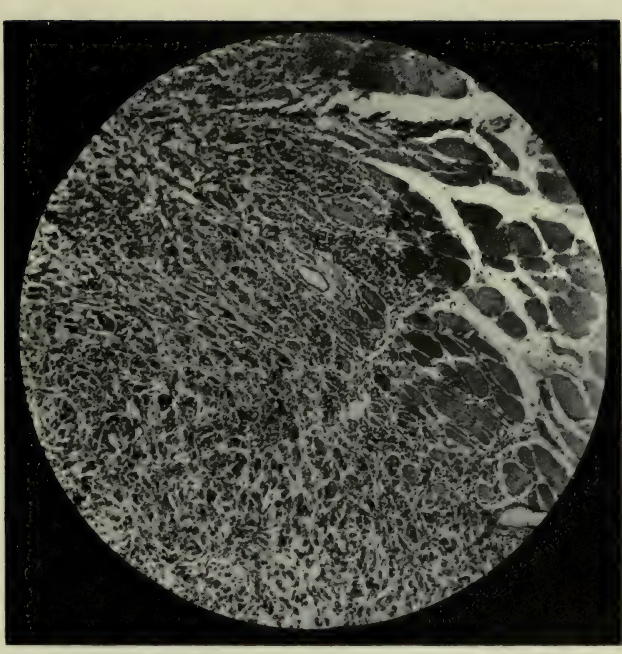
Fig. 24.



Carcinoma of the Kidney. From a rabbit.

This is a photograph of a section of the tumour shown in Fig. 23. It is a columnar-celled carcinoma.

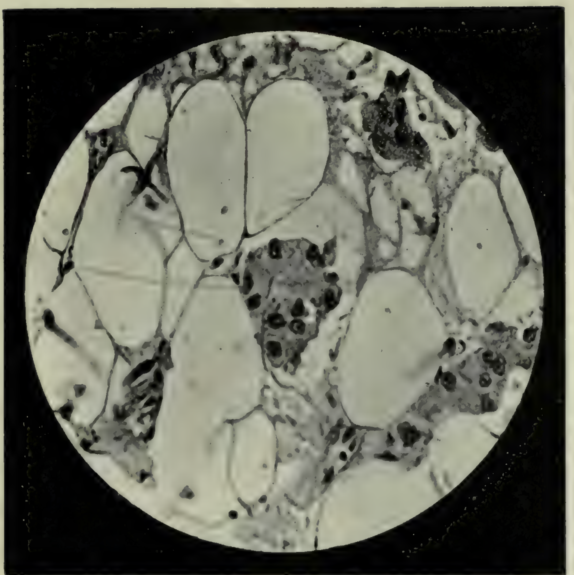
Fig. 25.



Carcinoma of the Breast, infiltrating the Pectoral Muscle.

This shows the carcinoma cells penetrating between the muscle fibres, causing them to undergo atrophy *in situ*.

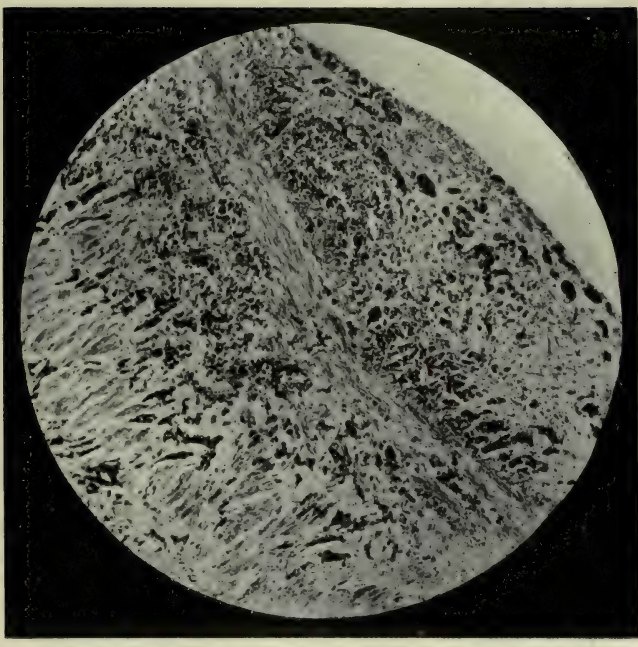
Fig. 26.



Carcinoma of the Breast invading fat.

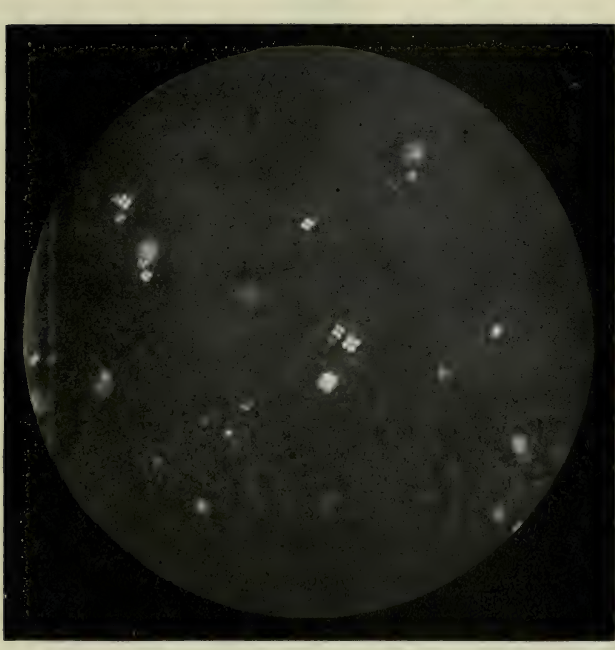
The carcinoma cells are proliferating within the fat cells.

Fig. 27.



Carcinoma infiltrating the wall of a large vein and forming growth in the intima.

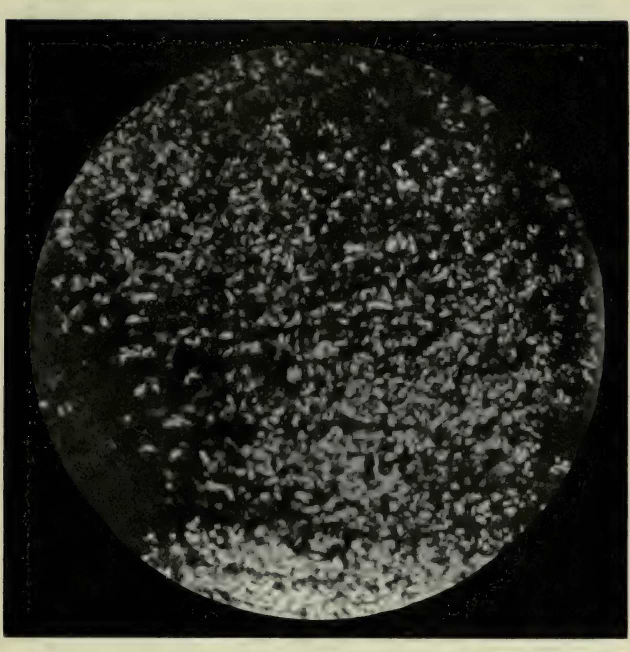
Fig. 28.



Carcinoma of the Breast. Polarised light.

The section has been heated and allowed to cool. Numerous anisotropic globules are seen appearing as bright globules divided into four parts by a dark cross. These were lying in and among the carcinoma cells which are not seen by this method of illumination.

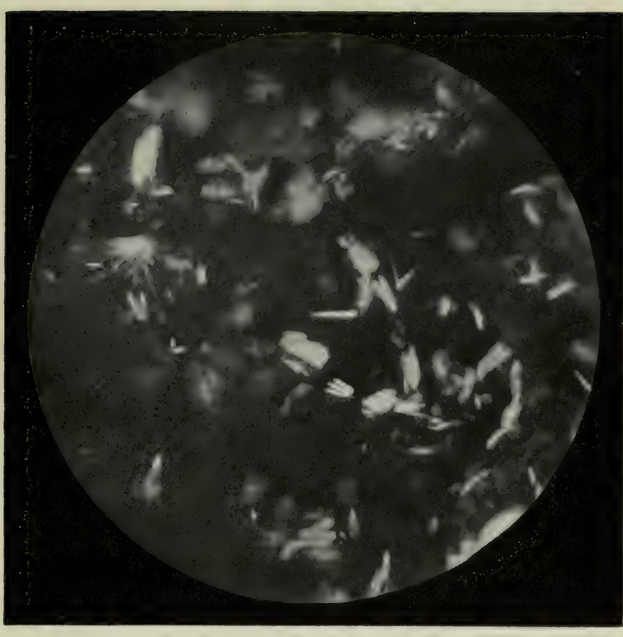
Fig. 29.



Normal Adrenal body. Polarised light. Low power.

The cells of the cortex are filled with numerous crystals appearing bright on a dark background.

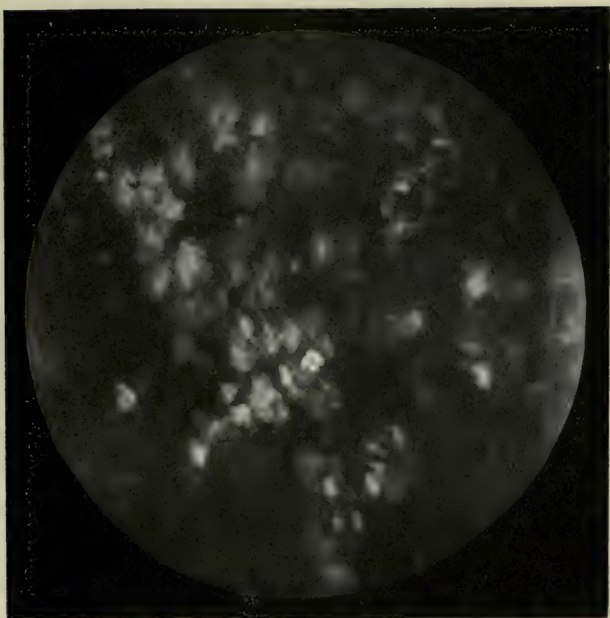
Fig. 30.



Normal Adrenal body. Polarised light. High power.

This is from the same section as Fig. 29 and shows the characters of the crystals in the adrenal cortex.

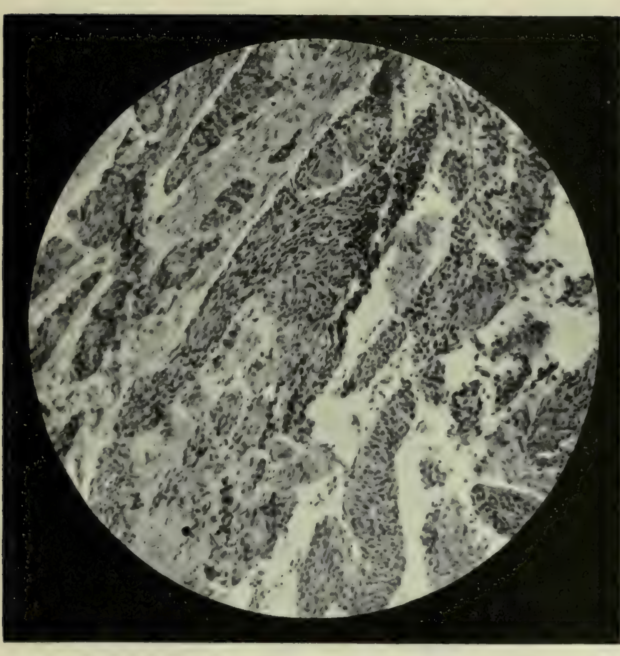
Fig. 31.



Normal Adrenal body. Polarised light. High power.

This is from the same section as Figs. 29, 30. The section has been heated and allowed to cool and the photograph shows the presence of anisotropic globules instead of crystals. Only one globule is in focus. Compare with Fig. 28.

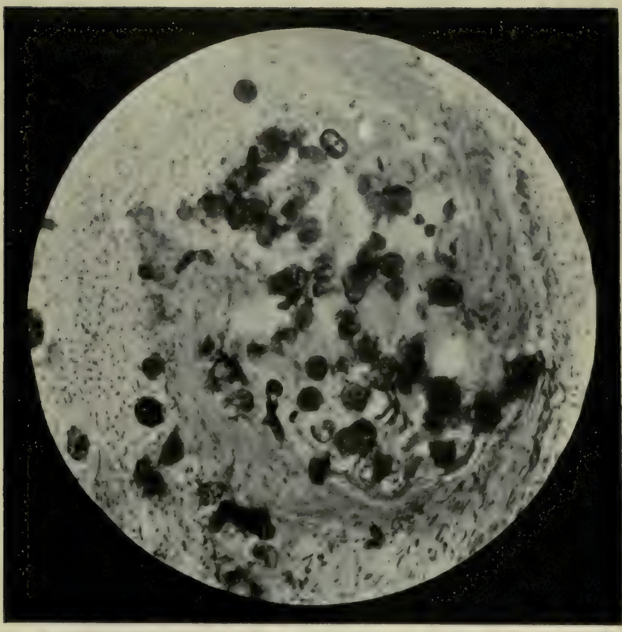
Fig. 32.



Bilharzial Carcinoma of the Bladder. (From Dr. Harris' specimen.)

This section shows a typical carcinoma of the bladder. No ova were found in the tumour itself.

Fig. 33.



Bilharzial Carcinoma of the Bladder. (From Dr. Harris' specimen.)

This section is from the connective tissue in the neighbourhood of the tumour and shows numerous ova.

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